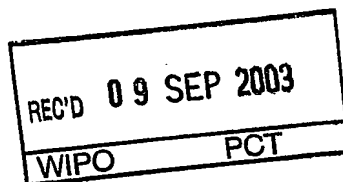




Europäisches
Patentamt

European
Patent Office

PCT 03/19890
Office européen
des brevets 10/522227
25 JAN 2005



Bescheinigung

Certificate

Attestation

Die angehefteten Unterla-
gen stimmen mit der
ursprünglich eingereichten
Fassung der auf dem näch-
sten Blatt bezeichneten
europäischen Patentanmel-
dung überein.

The attached documents
are exact copies of the
European patent application
described on the following
page, as originally filed.

Les documents fixés à
cette attestation sont
conformes à la version
initialement déposée de
la demande de brevet
européen spécifiée à la
page suivante.

Patentanmeldung Nr. Patent application No. Demande de brevet n°

02380178.0

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN
COMPLIANCE WITH
RULE 17.1(a) OR (b)

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

BEST AVAILABLE COPY



Anmeldung Nr:
Application no.: 02380178.0
Demande no:

Anmeldetag:
Date of filing: 09.08.02
Date de dépôt:

Anmelder/Applicant(s)/Demandeur(s):

ELI LILLY AND COMPANY
Lilly Corporate Center
Indianapolis, Indiana 46285
ETATS-UNIS D'AMERIQUE

Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se référer à la description.)

Kinase inhibitors

In Anspruch genommene Priorität(en) / Priority(ies) claimed / Priorité(s)
revendiquée(s)
Staat/Tag/Aktenzeichen/State/Date/File no./Pays/Date/Numéro de dépôt:

Internationale Patentklassifikation/International Patent Classification/
Classification internationale des brevets:

C07D333/00

Am Anmeldetag benannte Vertragsstaaten/Contracting states designated at date of
filing/Etats contractants désignées lors du dépôt:

AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LI LU MC NL PT SE SK TR

KINASE INHIBITORS

BACKGROUND OF THE INVENTION

5 The p38 kinase is a mitogen-activated protein (MAP) kinase that belongs to the serine/threonine kinase superfamily. This kinase is activated by extracellular stresses such as heat, UV light, and osmotic stress, as well as by inflammatory stimuli such as lipopolysaccharide. When activated, p38 kinase phosphorylates intracellular protein substrates that regulate the biosynthesis of the pro-inflammatory cytokines tumor necrosis factor α (TNF- α) and interleukin-1 β (IL-1 β). These cytokines are implicated in the pathology of a number of chronic inflammatory disorders (Lee, *et al.*, Ann. N.Y. Acad. Sci., 696, 149-170 (1993); Muller-Ladner, Curr. Opin. Rheumatol., 8, 210-220 (1996)), cardiovascular and central nervous system disorders (Salituro, *et al.*, Current Medicinal Chemistry, 6, 807-823 (1999)), and autoimmune disorders (Pargellis, *et al.*, Nature Structural Biology, 9(4), 268-272 (2002)).

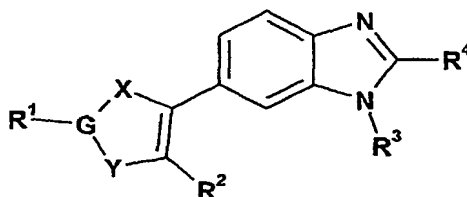
15 A number of compounds within the pyridinylimidazole (WO9621452, WO9725045, US5656644, US5686455, US5717100, WO9712876, WO9821957, WO9847892, WO99903837, WO9901449, WO0061576, WO0172737) and pyrimidinylimidazole (WO9725048, WO9901452, WO9725046, WO9932121, WO9901131, WO9901130, WO9901136, WO9807452, WO9747618, WO9856788, WO9857996)

20 structural platforms have been identified as inhibitors of p38 kinase or as cytokine inhibitors. Selective inhibitors of p38 kinase are known to suppress the expression of TNF- α and IL-1 β (McKenna, *et al.*, J. Med. Chem., 45(11), 2173-2184 (2002)). Anti-inflammatory activity for compounds within the pyrimidinylimidazole structural platform has been reported (Lantos, *et al.*, J. Med. Chem., 27, 72-75 (1984)), and a number of

25 inhibitors of p38 kinase are under active investigation for the treatment of a variety of disorders (Boehm and Adams, Exp. Opin. Ther. Patents, 10(1), 25-37 (2000)). The present invention provides new inhibitors of p38 kinase useful for the treatment of conditions resulting from excessive cytokine production.

BRIEF SUMMARY OF THE INVENTION

The present invention provides compounds of Formula I:



I

where:

R¹ is hydrogen, C₁-C₄ alkyl, 1-(C₁-C₄ alkoxy carbonyl)ethen-2-yl, phenyl optionally substituted with one or two substituents individually selected from the group consisting of halo, nitro, C₁-C₄ alkoxy, C₂-C₄ alkoxy substituted with piperidin-1-yl, and —
 10 NR⁵R⁶, pyridinyl, thiazolyl, or piperidin-4-yl optionally substituted at the 1-position with C₁-C₄ alkoxy carbonyl or (C₁-C₄ alkylene)-R⁷;

R² is phenyl optionally substituted with halo or trifluoromethyl;

R³ is hydrogen or (C₁-C₄ alkyl)sulfonyl;

R⁴ is halo or —NR⁸R⁹

15 R⁵ and R⁶ are individually at each occurrence selected from hydrogen or C₁-C₄ alkyl;

R⁷ is hydrogen, hydroxy, trifluoromethyl, or phenyl;

R⁸ is hydrogen or C₁-C₄ alkyl;

R⁹ is hydrogen, C₁-C₄ alkyl, or benzyl;

20 X-G-Y is —N=C-N(R¹⁰)—, —N(R¹¹)-C=N—, or —S-C=N—;

R¹⁰ is hydrogen or C₁-C₄ alkyl;

R¹¹ is hydrogen, cyclohex-1-yl optionally substituted in the 4-position with hydroxy, amino, N-[C₁-C₄ alkoxy carbonyl]amino, oxo, or ethylene glycol ketal, (C₁-C₄ alkylene)-R¹², piperidin-4-yl optionally substituted at the 1-position with C₁-C₄ alkyl or
 25 C₁-C₄ alkoxy carbonyl, or 2,2,6,6-tetramethylpiperidin-4-yl;

R¹² is hydrogen, hydroxy, C₁-C₄ alkoxy, C₁-C₄ alkoxy carbonyl, N-[C₁-C₄ alkoxy carbonyl]amino, C₃-C₆ cycloalkyl, tetrahydropyran-4-yl, morpholin-4-yl, or phenyl optionally substituted with one or two substituents individually selected from halo; provided that when X-G-Y is —N(R¹¹)-C=N—, then at least one of R¹ and R¹¹ is hydrogen or
 30 C₁-C₄ alkyl; or a pharmaceutically acceptable salt thereof.

The present invention provides a method of inhibiting p-38 kinase in a mammal comprising administering to a mammal in need of such treatment an effective amount of a compound of Formula I.

5 The present invention also provides a method of suppressing the production of tumor necrosis factor α (TNF- α) in a mammal comprising administering to a mammal in need of such treatment an effective amount of a compound of Formula I.

The present invention also provides a method of suppressing the production of interleukin-1 β (IL-1 β) in a mammal comprising administering to a mammal in need of such treatment an effective amount of a compound of Formula I.

10 The present invention further provides a method of treating conditions resulting from excessive cytokine production in a mammal comprising administering to a mammal in need of such treatment a cytokine-suppressing amount of a compound of Formula I.

The present invention also provides a method of treating susceptible neoplasms in a mammal comprising administering to a mammal in need of such treatment an
15 oncolytically effective amount of a compound of Formula I.

The present invention also provides a pharmaceutical formulation comprising a compound of Formula I, in combination with a pharmaceutically acceptable carrier, diluent or excipient.

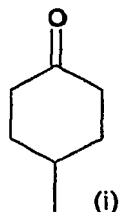
This invention also provides the use of a compound of Formula I for the
20 manufacture of a medicament for the inhibition of p38 kinase. Additionally, this invention provides a pharmaceutical formulation adapted for the inhibition of p38 kinase containing a compound of Formula I. Furthermore, this invention provides the use of a compound of Formula I for the manufacture of a medicament for the treatment of conditions resulting from excessive cytokine production. This invention also provides a
25 pharmaceutical formulation adapted for the treatment of conditions resulting from excessive cytokine production containing a compound of Formula I. Additionally, this invention provides the use of a compound of Formula I for the manufacture of a medicament for the treatment of susceptible neoplasms.

DETAILED DESCRIPTION OF THE INVENTION

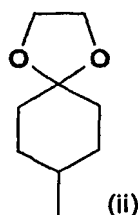
The general chemical terms used in the formulae above have their usual meanings. For example, the term "C₁-C₄ alkyl" includes methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, and tert-butyl moieties. The term "C₁-C₄ alkoxy" is taken to mean a C₁-C₄ alkyl group linked to the parent molecule through an oxygen atom, and includes the groups methoxy, ethoxy, isopropoxy, and the like. The term "halo" includes fluoro, chloro, bromo, and iodo.

The term "(C₁-C₄ alkylene)-R⁷" is taken to mean a linear or branched alkylene chain substituted at any carbon atom with the variable R⁷ and includes, for example, linear or branched alkyl chains, benzyl, and α -methylbenzyl moieties. Likewise, the term "(C₁-C₄ alkylene)-R¹²" is taken to mean a linear or branched alkylene chain substituted at any carbon atom with the variable R¹² and includes, for example, linear or branched alkyl chains, benzyl, and α -methylbenzyl moieties.

The term "cyclohex-1-yl optionally substituted in the 4-position with oxo" is taken to mean cyclohexan-4-on-1-yl that is of formula (i):



Likewise the term "cyclohex-1-yl optionally substituted in the 4-position with ethylene glycol ketal" is taken to mean the 1,4-dioxaspiro[4.5]dec-8-yl moiety which is the cyclic ketal of ethylene glycol and the compound of formula (i) as represented by formula (ii):



The term "p-38 kinase" is taken to mean the p-38 α and/or p-38 β kinase isoforms.

The term "suppressing the production of TNF- α (IL-1 β , cytokine)" is taken to mean decreasing of excessive in vivo levels of TNF- α , IL-1 β , or another cytokine in a mammal to normal or sub-normal levels. This may be accomplished by inhibition of the in vivo release of TNF- α , IL-1 β , or another cytokine by all cells, including macrophages; by down regulation, at the genomic level, of excessive in vivo levels of TNF- α , IL-1 β , or

another cytokine in a mammal to normal or sub-normal levels; by inhibition of the synthesis of TNF- α , IL-1 β , or another cytokine as a posttranslational event; or by a down regulation of TNF- α , IL-1 β , or another cytokine at the translational level.

5 The skilled artisan will appreciate that certain compounds of Formula I contain at least one chiral center. The present invention contemplates all individual enantiomers or diastereomers, as well as mixtures of the enantiomers and diastereomers of said compounds including racemates. It is preferred that compounds of Formula I containing at least one chiral center exist as single enantiomers or diastereomers. The single enantiomers or diastereomers may be prepared beginning with chiral reagents or by
10 stereoselective or stereospecific synthetic techniques. Alternatively, the single enantiomers or diastereomers may be isolated from mixtures by standard chiral chromatographic or crystallization techniques. Furthermore, certain compounds of Formula I may exist as the geometric cis- and trans- isomers. The present invention contemplates all individual geometric isomers as well as mixtures of the geometric
15 isomers of said compounds. It is preferred that compounds of Formula I exist as single geometric isomers. The individual isomers may be prepared selectively by methods known to the skilled artisan, or mixtures of the isomers may be separated by standard chromatographic or crystallization techniques.

It will be understood by the skilled reader that most or all of the compounds of the
20 present invention are capable of forming salts. In all cases, the pharmaceutically acceptable salts of all of the compounds are included in the names of them. The compounds of the present invention are amines, and accordingly react with any of a number of inorganic and organic acids to form pharmaceutically acceptable acid addition salts. Preferred pharmaceutically acceptable salts are those formed with hydrochloric acid
25 and methanesulfonic acid.

While all of the compounds of Formula I are useful inhibitors of p-38 kinase, certain classes of compounds are preferred. The following paragraphs describe such preferred classes:

- a) R¹ is hydrogen;
- 5 b) R¹ is 1-(ethoxycarbonyl)ethen-2-yl;
- c) R¹ is phenyl optionally substituted with one or two substituents individually selected from the group consisting of halo, nitro, C₁-C₄ alkoxy, and -NR⁵R⁶;
- d) R¹ is phenyl;
- 10 e) R¹ is phenyl substituted with chloro;
- f) R¹ is 2,6-difluorophenyl;
- g) R¹ is 4-methoxyphenyl;
- h) R¹ is phenyl substituted in the 4-position with -NR⁵R⁶;
- i) R¹ is 4-nitrophenyl;
- 15 j) R¹ is thien-2-yl;
- k) R¹ is 5-nitrothien-2-yl;
- l) R¹ is 5-aminothien-2-yl;
- m) R¹ is thiazol-2-yl;
- n) R¹ is pyridin-4-yl;
- 20 o) R¹ is piperidin-4-yl;
- p) R¹ is 1-methylpiperidin-4-yl;
- q) R² is phenyl;
- r) R² is 4-fluorophenyl;
- s) R² is 3-trifluoromethylphenyl;
- 25 t) R³ is isopropylsulfonyl;
- u) R⁴ is halo;
- v) R⁴ is chloro;
- w) R⁴ is -NH₂;
- x) R⁵ is hydrogen;
- 30 y) R⁵ is methyl;
- z) R⁶ is hydrogen;
- aa) R⁶ is methyl;
- bb) R⁵ and R⁶ are the same;
- cc) X-G-Y is -N=C-N(R¹⁰)-;
- 35 dd) X-G-Y is -N(R¹¹)-C=N-;
- ee) R¹⁰ is hydrogen;
- ff) R¹¹ is -CH₂-R¹²;

- gg) R¹¹ is piperidin-4-yl;
- hh) R¹¹ is 1-methylpiperidin-4-yl;
- ii) R¹¹ is cyclohexan-1-on-4-yl;
- jj) R¹¹ is 1-hydroxycyclohex-4-yl;
- 5 kk) R¹¹ is 1-aminocyclohex-4-yl;
- ll) R¹¹ is cyclohexyl;
- mm) R¹¹ is tetrahydropyran-4-yl;
- nn) R¹² is hydrogen;
- oo) R¹² is methoxy;
- 10 pp) R¹² is cyclopropyl;
- qq) R¹² is morpholin-4-yl;
- rr) the compound of Formula I is a free base;
- ss) the compound of Formula I is a pharmaceutically acceptable salt;
- tt) the compound of Formula I is the hydrochloride salt;
- 15 uu) the compound of Formula I is the methanesulfonate salt.

It will be understood that the above classes may be combined to form additional preferred classes.

The compounds of Formula I are inhibitors of p38 kinase. Thus, the present invention also provides a method of inhibiting p38 kinase in a mammal that comprises
20 administering to a mammal in need of said treatment a p38 kinase-inhibiting amount of a compound of Formula I. It is preferred that the mammal to be treated by the administration of the compounds of Formula I is human.

As inhibitors of p38 kinase, the compounds of the present invention are useful for suppressing the production of the pro-inflammatory cytokines tumor necrosis factor α
25 (TNF- α) and interleukin-1 β (IL-1 β), and therefore for the treatment of disorders resulting from excessive cytokine production. The present compounds are therefore believed to be useful in treating inflammatory disorders, including eczema, atopic dermatitis, rheumatoid arthritis, osteoarthritis, inflammatory bowel disease, and toxic shock syndrome. The compounds of the present invention are also believed to be useful in the treatment of
30 cardiovascular disorders, such as acute myocardial infarction, chronic heart failure, atherosclerosis, viral myocarditis, cardiac allograft rejection, and sepsis-associated cardiac dysfunction. Furthermore, the compounds of the present invention are also believed to be useful for the treatment of central nervous system disorders, such as meningococcal meningitis, Alzheimer's disease, Parkinson's disease, and multiple sclerosis.

35 Most solid tumors increase in mass through the proliferation of malignant cells and stromal cells, including endothelial cells. In order for a tumor to grow larger than 2-3 millimeters in diameter, it must form a vasculature, a process known as angiogenesis.

Suppression of tumor-induced angiogenesis by angiostatin and endostatin has been reported to result in antitumor activity (O'Reilly, *et al.*, Cell, **88**, 277-285 (1997)). The selective p38 kinase inhibitor SB22025 has been shown to inhibit angiogenesis (J.R. Jackson, *et al.*, J. Pharmacol. Exp. Therapeutics, **284**, 687 (1998)). Because angiogenesis is a critical component of the mass expansion of most solid tumors, the development of new p38 kinase inhibitors for the inhibition of this process represents a promising approach for antitumor therapy. This approach to antitumor therapy may lack the toxic side effects or drug resistance-inducing properties of conventional chemotherapy (Judah Folkman, Endogenous Inhibitors of Angiogenesis, The Harvey Lectures, Series 92, pages 65-82, Wiley-Liss Inc., (1998)).

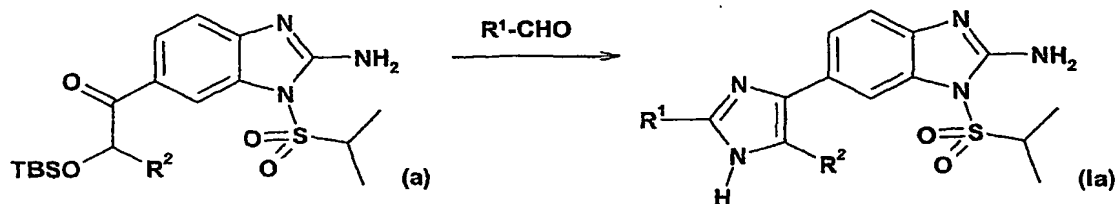
As inhibitors of p38 kinase the compounds of the present invention, therefore, are also useful for the treatment of susceptible neoplasms. A susceptible neoplasm is defined to be a neoplasm that depends upon p38 kinase for its survival, growth, or metastasis. Susceptible neoplasms include tumors of the brain, genitourinary tract, lymphatic system, stomach, larynx, and lung (U.S. Patent #5,717,100). Preferably, the term "susceptible neoplasms" as used in the present application includes human cancers including non-small cell lung carcinoma (A. Greenberg, *et al.*, Am. J. Respir. Cell Mol. Biol., **26**, 558 (2002)), breast carcinoma (J. Chen, *et al.*, J. Biol. Chem., **276**, 47901 (2001); B. Salh, *et al.*, Int. J. Cancer, **98**, 148 (2002); and S. Xiong, *et al.*, Cancer Res., **61**, 1727 (2001)), gastric carcinoma (Y.D. Jung, *et al.*, Proc. Am. Assoc. Cancer Res., **43**, 9 (2002)), colorectal carcinomas (S. Xiong, *et al.*, Cancer Res., **61**, 1727 (2001)), and malignant melanoma (C. Denkert, *et al.*, Clin. Exp. Metastasis, **19**, 79 (2002)).

Inhibition of angiogenesis by suppression of TNF- α has also been taught to be useful in the inhibition or prevention of metastasis (U.S. Patent #6,414,150; U.S. Patent #6,335,336). Furthermore, suppression of TNF- α is indicated for the treatment and prevention of cachexia, a wasting syndrome experienced by about half of all cancer patients (T. Yoneda, *et al.*, J. Clin. Invest., **87**, 977 (1991)).

The compounds of the present invention can be prepared by a variety of procedures, some of which are illustrated in the Schemes below. It will be recognized by one of skill in the art that the individual steps in the following schemes may be varied to provide the compounds of Formula I. The particular order of steps required to produce the compounds of Formula I is dependent upon the particular compound being synthesized, the starting compound, and the relative lability of the substituted moieties. Some substituents have been eliminated in the following schemes for the sake of clarity and are not intended to limit the teaching of the schemes in any way.

Compounds of Formula I where X-G-Y is $-N=C-N(R^{10})-$ and R^4 is $-NH_2$ may be prepared as illustrated in the following scheme where "TBS" is defined to be *tert*-butyldimethylsilyl and variables R^1 and R^2 are as previously defined.

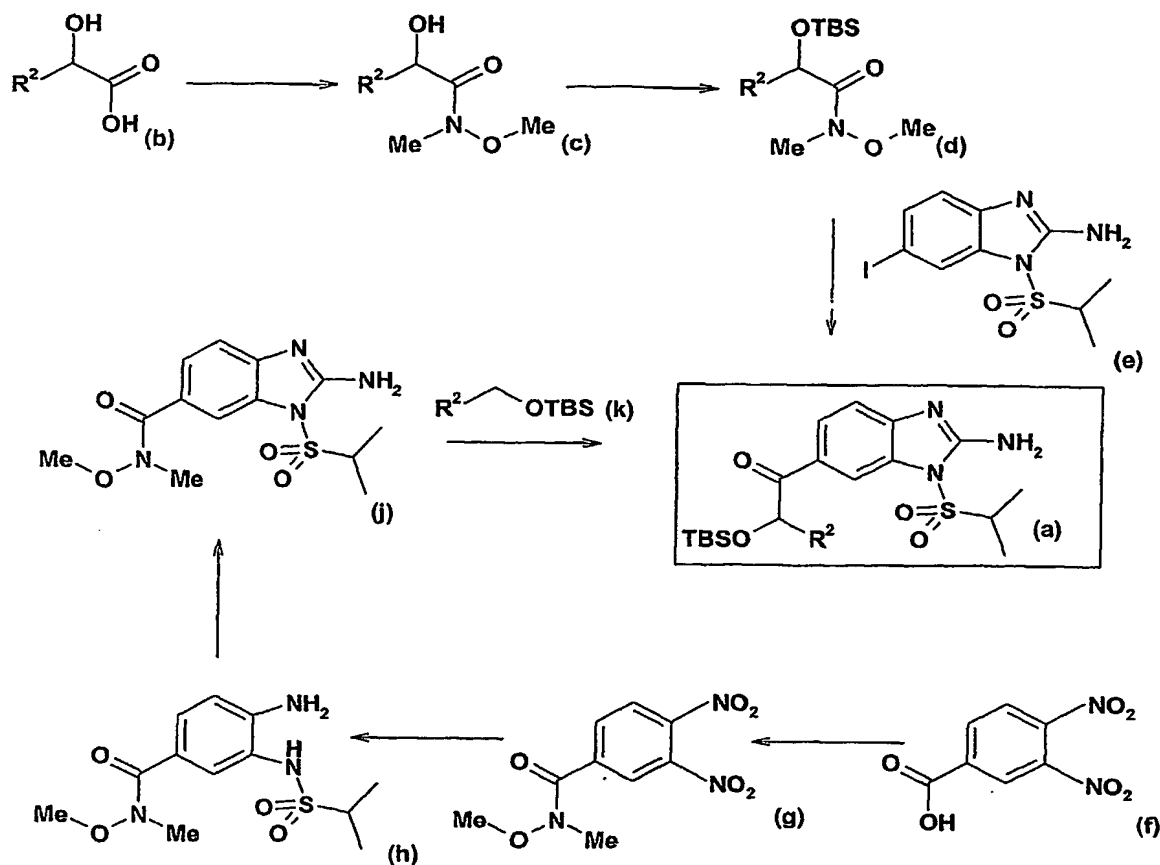
Scheme I



A mixture of the α -ketosilylether (a) is heated with an appropriate aldehyde in the presence of copper(II) acetate and ammonium acetate in a suitable solvent, typically acetic acid. The acid is neutralized and the desired imidazole (Ia) isolated by standard extractive and chromatographic techniques.

The requisite α -ketosilylether (a) may be prepared as described in the following scheme where "TBS" and variables R^2 is as previously defined.

Scheme II



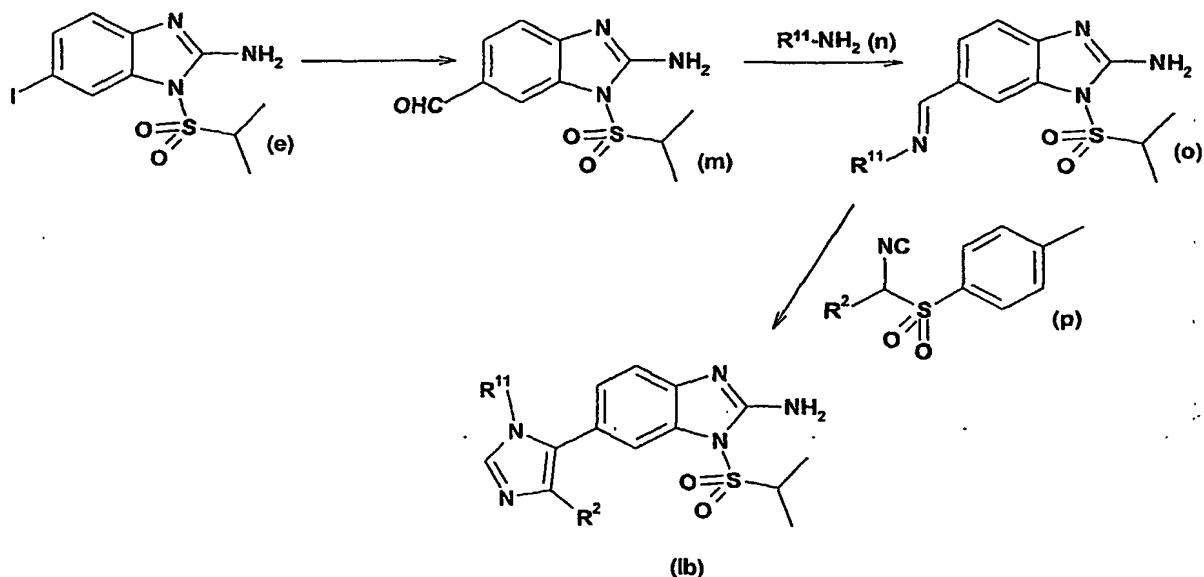
An appropriate α -hydroxyacid (b) is converted to the corresponding Weinreb amide (c) under standard conditions. Briefly, the α -hydroxyacid (b) is converted to the corresponding methyl ester and this ester is then reacted with N-methyl-O-methylhydroxyl-amine hydrochloride in the presence of trimethylaluminum in an appropriate solvent. The α -hydroxyamide (c) is then treated with *tert*-butyldimethylsilyl triflate in the presence of base under standard conditions to provide the α -silylether amide (d). Compound (d) is then coupled with 1-(isopropylsulfonyl)-2-amino-6-iodobenzimidazole (e) in the presence of isopropylmagnesium chloride to provide the desired compound (a) by the method of Tius, *et al.* (*Tetrahedron*, **56**, 3339-3351 (2000)). The requisite iodobenzimidazole (e) may be prepared from 2-aminobenzimidazole as described by Mitchell, *et al.* (*Journal of Organic Chemistry*, **63**, 5050-5058 (1998)).

Alternatively, 3,4-dinitrobenzoic acid (f) may be converted to the corresponding Weinreb amide (g) by converting the benzoic acid to the corresponding benzoyl halide, preferably by reaction with oxalyl chloride, and then reacting the benzoyl chloride with N-methyl-O-methylhydroxylamine in the presence of a suitable base, typically pyridine, to provide the corresponding amide. The amide (g) is then subjected to catalytic

hydrogenation conditions to provide the corresponding diamine that is then treated with isopropylsulfonyl chloride in the presence of a base, typically pyridine, to provide the corresponding sulfonamide (h). This sulfonamide is first treated with base and then reacted with cyanogen bromide in a suitable solvent to provide the aminobenzimidazole (j). The aminobenzimidazole (j) is reacted with the anion generated from the silyl ether (k) and *tert*-butyllithium to provide the desired intermediate (a). The requisite silyl ether may be prepared from the corresponding alcohol under standard conditions (see, Greene, et al., Protective Groups in Organic Synthesis, John Wiley and Sons Ed., 1981).

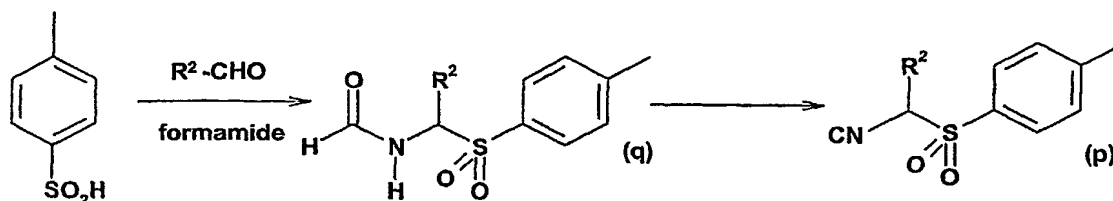
Compounds of Formula I where X-G-Y is $-N(R^{11})-C=N-$ and R^4 is $-NH_2$ may be prepared as described in the following scheme where variables R^1 and R^{11} are as previously defined.

Scheme III



The dianion of 1-(isopropylsulfonyl)-2-amino-6-iodobenzimidazole (e) is prepared by sequential treatment with phenyllithium followed by *tert*-butyllithium at low temperature. The dianion is quenched with dimethylformamide and the corresponding aldehyde (m) is isolated under standard conditions. This aldehyde is then reacted with an appropriate amine (n) in a suitable solvent, typically dimethylformamide, to form the corresponding imine (o). This imine is then reacted with an appropriately substituted p-toluenesulfonylmethyl isocyanate (p) in methanol and *tert*-butylamine at reflux to provide the desired compound (Ib). The requisite amines (n) are either commercially available or may be prepared by methods well known to the skilled artisan. The requisite p-toluenesulfonylmethyl isocyanates (p) may be prepared as described in the following scheme where the variable R^2 is as previously defined.

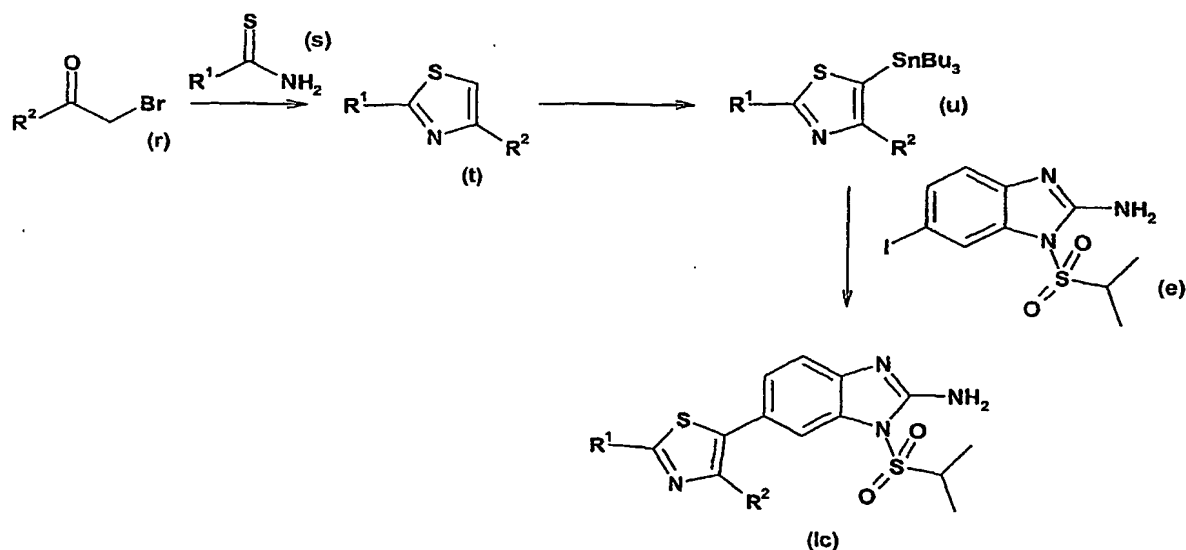
Scheme IV



5 A mixture of p-toluenesulfonic acid, formamide, and an appropriate aldehyde are combined and heated together in the presence of a suitable acid to provide the N-formyl p-toluenesulfonylmethylamine (q). The intermediate (q) is reacted with a suitable dehydrating agent, typically phosphorus oxychloride, to provide the isocyanide (p). The requisite aldehydes are either commercially available or may be prepared by standard methods well known in the art.

10 Compounds of Formula I where X-G-Y is $-\text{N-C=S}-$ and R^4 is $-\text{NH}_2$ may be prepared as illustrated in the following scheme where R^1 and R^2 are as previously defined.

Scheme V



An appropriate α -haloketone (r) is reacted with an appropriate thioamide (s) in a suitable solvent to provide thiazole (t). This thiazole is treated with *n*-butyllithium and the resulting anion is reacted with tributyltin chloride to provide the tin derivative (u). This intermediate is coupled with 1-(isopropylsulfonyl)-2-amino-6-iodobenzimidazole (e) in the presence of a palladium catalyst under standard conditions to provide the desired compound (Ic).

The requisite α -haloketones are either commercially available or may be prepared by standard conditions from the corresponding carbonyl compound, for example, as described by House (H.O. House, *Modern Synthetic Reactions*, W.A. Benjamin, Inc., Menlo Park, California (1972), pages 459-478) and Larock (R.C. Larock, *Comprehensive Organic Transformations*, VCH Publishers, Inc., New York, New York (1989), pages 369-471, 755). The requisite thioamides are either commercially available or may be prepared by standard methods well known to the skilled artisan, for example, by treatment of an appropriate amide with [2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide] (Lawesson's Reagent).

Many of the compounds of the present invention are not only inhibitors of p38 kinase, but are also useful intermediates for the preparation of additional compounds of the present invention. For example, primary and secondary amines may be acylated, alkylated or coupled with carboxylic acids or amino acids under standard peptide coupling conditions. Furthermore, ester moieties may be reduced to the corresponding alcohols or converted to amides under standard conditions. Alcohols may be activated and displaced by a number of nucleophiles to provide other compounds of the invention. Such leaving groups include but are not limited to halides, oxonium ions, alkyl

perchlorates, ammonioalkanesulfonate esters, alkyl fluorosulfonates, nonaflates, tresylates, triflates, and sulfonic esters, preferably the mesylate or tosylate. Techniques for the introduction of these groups are also well known to the skilled artisan; see, for example, March, Advanced Organic Chemistry, 5th Ed., John Wiley and Sons, New York, pg. 445-449 (2001). Additionally, the 2-amino moiety of the benzimidazole nucleus may be diazotized and displaced to provide the corresponding halo derivatives under standard conditions. These compounds may then be reacted with a variety of amines under standard conditions to provide additional compounds of Formula I.

The skilled artisan will also appreciate that not all of the substituents in the compounds of Formula I will tolerate certain reaction conditions employed to synthesize the compounds. These moieties may be introduced at a convenient point in the synthesis, or may be protected and then deprotected as necessary or desired. The skilled artisan will appreciate that the protecting groups may be removed at any convenient point in the synthesis of the compounds of the present invention. Methods for introducing and removing nitrogen and oxygen protecting groups are well known in the art; see, for example, Greene and Wuts, Protective Groups in Organic Synthesis, 3rd Ed., John Wiley and Sons, New York, Chapter 7 (1999). Furthermore, the skilled artisan will appreciate that in many circumstances, the order in which moieties are introduced is not critical. The particular order of steps required to produce the compounds of Formula I is dependent upon the particular compound being synthesized, the starting compound, and the relative lability of the substituted moieties.

Preparation 1

1-(isopropylsulfonyl)-2-amino-6-formylbenzimidazole

Add phenyllithium (750 mL, 1.8 M in cyclohexane/ether, 70/30) over 1 hour to a solution of 1-(isopropylsulfonyl)-2-amino-6-iodobenzimidazole (150 g, 0.41 mol) in tetra-hydrofuran (5.6 L) at -76°C. Stir for 15 minutes and then add tert-butyllithium (750 mL, 1.7M in pentane). After 1 hour add dimethylformamide (250 mL) slowly over one hour and then warm to 0°C. Quench by pouring the reaction mixture into a mixture of cold saturated aqueous ammonium chloride (500 g, 5L) and concentrated hydrochloric acid (300 mL). Separate the layers, wash the organic phase with water and then concentrate under reduced pressure. Slurry the residue in methanol (500 mL), filter the yellow precipitate, and dry to provide 85 g (76%) of the title compound.

¹H-NMR (DMSO-d₆): δ 9.89 (s, 1H), 7.97 (s, 1H), 7.76 (d, 1H), 7.43 (s, 2H), 7.37 (d, 1H), 3.98 (m, 1H), 1.35 (m, 6H).

Preparation 2

α -(p-toluenesulfonyl)benzylisocyanideN-[formyl] α -(p-toluenesulfonyl)benzylamine

5 Add concentrated hydrochloric acid (3 mL) dropwise to a solution of p-toluenesulfinic acid sodium salt in water (20 mL) and tert-butyl methyl ether (10 mL). Stir for 10 minutes and then separate the layers. Wash the organic layer with saturated aqueous sodium chloride, dry over sodium sulfate and concentrate under reduced pressure to provide 5 g of p-toluenesulfinic acid. Combine this acid with benzaldehyde (4.75 g, 44.8 mmol), formamide (4.9 g, 0.11 mol), and camphorsulfonic acid (0.86 g, 3.7 mmol) and heat to 60°C for 18 hours. Remove the reaction from the heat and slurry the white solid in 10 3:1 hexanes:methanol. Filter the slurry to provide 7.6 g (82%) of the desired product as a white solid.

¹H-NMR (DMSO-d₆): δ 9.75 (d, 1H), 7.98 (s, 1H), 7.69 (d, 2H), 7.53 (d, 2H), 7.39 (m, 5H), 6.36 (d, 1H), 2.38 (s, 1H).

15 Dehydration

Cool a solution of N-[formyl] α -(p-toluenesulfonyl)benzylamine (7.0 g, 0.024 mol) in dimethoxyethane (200 mL) to -10°C. Add phosphorus oxychloride (5.6 mL, 0.06 mol) followed by the dropwise addition of triethylamine (16.8 mL, 0.12 mol) in dimethoxyethane (10 mL) maintaining a reaction temperature below -5°C. Warm the 20 reaction mixture gradually over 1 hour, add water and extract with ethyl acetate. Separate the layers, wash the organic phase with saturated aqueous sodium bicarbonate, dry over sodium sulfate, and concentrate under reduced pressure to provide 6.5 g of the title compound.

MS(ES⁺): m/z = 270.1.

The compounds of Preparations 3-4 were prepared essentially as described in Preparation 2.

Prep.	Compound	MS(ES ⁺): <i>m/z</i> =
3	α -(<i>p</i> -toluenesulfonyl)-4-fluorobenzylisocyanide	288.1
4	α -(<i>p</i> -toluenesulfonyl)- α -(thien-3-yl)methylisocyanide	276.0

Preparation 5

5 N-[1-(ethoxycarbonyl)piperidin-4-yl] (1-(isopropylsulfonyl)-2-amino-6-formylbenzimidazole)imine

Combine 1-(isopropylsulfonyl)-2-amino-6-formylbenzimidazole (1.0 g, 3.7 mmol) and 1-(ethoxycarbonyl)-4-aminopiperidine (0.64 g, 3.7 mmol) in dimethylformamide (5 mL) and stir at room temperature over night. Dilute the reaction mixture with ethyl acetate (50 mL) and wash sequentially with water (2 x 10 mL) and saturated aqueous sodium chloride (2 x 10 mL). Dry the remaining organic phase over sodium sulfate and concentrate under reduced pressure to provide 1.5 gm (95%) of the title compound. MS(ES⁺): *m/z* = 422.2.

The compounds of Preparations 6-25 were prepared essentially as described in

15 Preparation 5.

Prep.	Compound	MS(ES ⁺): <i>m/z</i> =
6	N-[1-(benzyl)piperidin-4-yl] (1-(isopropylsulfonyl)-2-amino-6-formylbenzimidazole)imine	439.9
7	N-[2-(morpholin-4-yl)eth-1-yl] (1-(isopropylsulfonyl)-2-amino-6-formylbenzimidazole)imine	379.9
8	N-[3-(morpholin-4-yl)prop-1-yl] (1-(isopropylsulfonyl)-2-amino-6-formylbenzimidazole)imine	393.9
9	N-[1,4-dioxaspiro[4.5]dec-8-yl] (1-(isopropylsulfonyl)-2-amino-6-formylbenzimidazole)imine	406.9
10	N-[4-hydroxycyclohex-1-yl] (1-(isopropylsulfonyl)-2-amino-6-formylbenzimidazole)imine	364.9
11	N-[cyclohexyl] (1-(isopropylsulfonyl)-2-amino-6-formylbenzimidazole)imine	348.9
12	N-[methyl] (1-(isopropylsulfonyl)-2-amino-6-formylbenzimidazole)imine	280.9
13	N-[3-(phenyl)prop-1-yl] (1-(isopropylsulfonyl)-2-amino-6-formylbenzimidazole)imine	384.9
14	N-[2-(methoxy)eth-1-yl] (1-(isopropylsulfonyl)-2-amino-6-formylbenzimidazole)imine	324.9
15	N-[2-((<i>tert</i> -butoxycarbonyl)amino)eth-1-yl] (1-(isopropylsulfonyl)-2-amino-6-formylbenzimidazole)imine	409.9
16	N-[tetrahydropyran-4-yl] (1-(isopropylsulfonyl)-2-amino-6-formylbenzimidazole)imine	350.9
17	N-[4-((<i>tert</i> -butoxycarbonyl)amino)cyclohex-1-yl] (1-(isopropylsulfonyl)-2-amino-6-formylbenzimidazole)imine	463.9

18	N-[2-hydroxyeth-1-yl] (1-(isopropylsulfonyl)-2-amino-6-formylbenzimidazole)imine	311.0
19	N-[(pyridin-4-yl)methyl] (1-(isopropylsulfonyl)-2-amino-6-formylbenzimidazole)imine	357.9
20	N-[2,4-difluorobenzyl] (1-(isopropylsulfonyl)-2-amino-6-formylbenzimidazole)imine	392.9
21	N-[4-fluorobenzyl] (1-(isopropylsulfonyl)-2-amino-6-formylbenzimidazole)imine	374.9
22	N-[2,2,6,6-tetramethylpiperidin-4-yl] (1-(isopropylsulfonyl)-2-amino-6-formylbenzimidazole)imine	406.0
23	N-[(pyridin-3-yl)methyl] (1-(isopropylsulfonyl)-2-amino-6-formylbenzimidazole)imine	357.9
24	N-[(pyridin-2-yl)methyl] (1-(isopropylsulfonyl)-2-amino-6-formylbenzimidazole)imine	357.9
25	N-[(cyclopropyl)methyl] (1-(isopropylsulfonyl)-2-amino-6-formylbenzimidazole)imine	321.0

Preparation 26

N-[methyl] N-[methoxy] 1-(isopropylsulfonyl)-2-aminobenzimidazole-6-carboxamide
N-[methyl]-N-[methoxy] 3,4-dinitrobenzamide

5 Cool a mixture of 3,4-dinitrobenzoic acid (195 g, 0.92 moles), 1.3 L of dry dichloromethane, and 2 mL dimethylformamide to -12°C under a nitrogen atmosphere. Add oxalyl chloride (134 ml, 1.54 moles) dropwise via addition funnel over 35 minutes and stir the reaction mixture at room temperature under a nitrogen atmosphere over night. Remove excess oxalyl chloride from the reaction mixture by repetitive cycles of

10 concentrating a dichloromethane solution of the reaction mixture under reduced pressure. Cool a mixture of the residue 1 L dichloromethane to -5°C under a nitrogen atmosphere and add N,O-dimethylhydroxylamine hydrochloride (98.7 g, 1.01 moles) followed by the careful addition of 209 mL (2.62 moles) of dry pyridine in portions. Stir the mixture at room temperature for 4 hours and then concentrate under reduced pressure. Suspend the

15 residue in 500 mL dichloromethane and concentrate under reduced pressure twice. Suspend the residue in 500 mL dichloromethane and filter. Store the filtrate at -13°C for 3 days, filter the solid and rinse with cold dichloromethane. Dilute the filtrate with water (40ml) and stored at -13°C again to provide a second crop. Dry the combined crops under reduced pressure to provide 182 g (77%) of the desired compound.

20 N-[methyl] N-[methoxy] 3,4-diaminobenzamide

Add 18.0 g of 10% weight Pd/C catalyst to a solution of N-[methyl] N-[methoxy] 3,4-dinitrobenzamide (182 g, 0.712 moles) in 900 mL tetrahydrofuran and 900 mL ethanol under a nitrogen atmosphere. Hydrogenate at room temperature for 6 hours under

25 60 p.s.i. Filter the mixture through Celite and concentrate the filtrate under reduced pressure. Suspend the residue in 500 mL dichloromethane, concentrate under reduced

pressure and dry the residue under reduced pressure to provide 135 g (97%) of the desired compound.

N-[methyl] N-[methoxy] 3-(isopropylsulfonyl)amino-4-aminobenzamide

- 5 Add dry pyridine (234 ml, 2.94 moles) to a cold (0 °C) solution of N-[methyl] N-[methoxy] 3,4-diaminobenzamide (135 g, 0.69 moles) in 1 liter of dry dichloromethane under a nitrogen atmosphere. Add isopropylsulfonyl chloride (85.4 ml 0.76 moles) at 0°C over 30 minutes, stir the mixture 0°C for another 30 minutes, and then at room temperature overnight. Concentrate the reaction mixture under reduced pressure and
- 10 partition the residue with 1 L diethyl ether and 1 L 5 N hydrochloric acid. Separate the layers, discard the diethyl ether layer, add ethyl acetate (1.5 L) to the aqueous layer and stir while adding solid sodium carbonate until pH = 6.5. Extract the aqueous layer using ethyl acetate, wash the combined organic layers, dry over magnesium sulfate and concentrate under reduced pressure. Subject the residue to silica gel chromatography
- 15 eluting with a gradient 65:3 ethyl acetate:hexane to 100% ethyl acetate to provide a 40% yield of the desired compound.

Imidazole Ring Formation

- 20 Add 55 mL 5 N sodium hydroxide over 1 hour to a suspension of N-[methyl] N-[methoxy] 3-(isopropylsulfonyl)amino-4-aminobenzamide (83 g, 0.28 moles) in 550 ml of isopropyl alcohol and 28 mL of water. Stir the reaction mixture for an additional hour and then cool to 3 °C. Add cyanogen bromide (29.0 g, 0.27 moles) in portions and stir at room temperature over night, at reflux for 5 hours, and then at room temperature over night. Add ethyl acetate (1.5 L), stir vigorously and then filter the resulting suspension.
- 25 Wash the filtrate with saturated aqueous sodium chloride, dry over magnesium sulfate and then concentrate to about ¼ volume. Filter the suspension and wash the solid with cold ethyl acetate. Concentrate the filtrate under reduced pressure and crystallize the residue from ethyl acetate to provide a second crop. The combined crops provide a 60% yield of the title compound.
- 30 MS(FD⁻): m/z = 326 (M+1)

Preparation 27

N-[methyl] N-[methoxy] 2-(tert-butyldimethylsilyl)oxy-2-(4-fluorophenyl)acetamide
Methyl p-fluoromandelate

- 35 Add potassium carbonate (12 g, 87 mmol) followed by iodomethane (7.37 mL, 118 mmol) to a 0°C solution of p-fluoromandelic acid (79 mmol, 13.4 g) in 160 mL dry dimethylformamide under a nitrogen atmosphere. Stir the resulting mixture at 0°C for 1

hour and at room temperature over night. Pour the reaction mixture over ice, dilute with water and ethyl acetate, and extract the aqueous layer three times with ethyl acetate.

Wash the combined organic layers with cold water and saturated aqueous sodium chloride, dried over sodium sulfate and concentrate under reduced pressure to provide
5 12.7 gm (87%) of the desired compound as a light yellow oil.

N-[methyl] N-[methoxy] 2-hydroxy-2-(4-fluorophenyl)acetamide

Cool a mixture of N-methyl-O-methyl hydroxylamine hydrochloride (118 mmol) and toluene (125 mL) to -5°C. Slowly add trimethylaluminum (2 M in heptane, 59.2 mL,
10 118 mmol) to the mixture over 20 minutes, maintaining the reaction temperature from -1 to 8 °C. After about 5 minutes slowly warm the mixture to room temperature and stir for 1.5 hours. Add a solution of methyl p-fluoromandelate (11.1 g, 60 mmol) in 75 mL of toluene over 30 min without external cooling. Cool the reaction to 0°C and quench with
15 10% hydrochloric acid. Extract with ethyl acetate (4 X 250 mL). Wash the combined ethyl acetate layers sequentially with water and saturated aqueous sodium chloride, dry over sodium sulfate and concentrate under reduced pressure to provide 12.1 g (82%) of the desired compound.

O-Silylation

20 Add triethylamine (17.2 mL, 123 mmol) followed by tert-butyldimethylsilyl triflate (20.8 mL, 90 mmol) to a 0°C) solution of N-[methyl] N-[methoxy] 2-hydroxy-2-(4-fluorophenyl)acetamide (12.1 g, 62 mmol) in 180 mL of dichloromethane under a nitrogen atmosphere. Stir the reaction mixture at 0°C for 1 hour and at room temperature for 4 hours. Add a saturated aqueous solution of ammonium chloride and dilute with
25 diethyl ether. Wash the organic layer sequentially with water and saturated aqueous sodium chloride, dry over sodium sulfate, and concentrate under reduced pressure. Subject the residue to silica gel chromatography, eluting with 9:1 hexane:ethyl acetate to provide the title compound as a yellow oil in 55% yield.

30

Preparation 28

N-[methyl] N-[methoxy] 2-(tert-butyldimethylsilyl)oxy-2-(4-(trifluoromethyl)phenyl)acetamide

Beginning with p-(trifluoromethyl)mandelic acid, the title compound may be prepared essentially as described in Preparation 27.

35

Preparation 29

1-(isopropylsulfonyl)-2-amino-6-(α -((*tert*-butyldimethylsilyl)oxy)- α -(phenyl)acetyl)-benzimidazole

- Add isopropylmagnesium chloride (2.0 M in THF, 235 mL, 470 mmol) over 15 minutes to a solution of 1-(isopropylsulfonyl)-2-amino-6-iodobenzimidazole (42.9 g, 118 mmol) in tetrahydrofuran (850 mL) at -70°C under a nitrogen atmosphere. Stir for 1 hour at 0°C and then add a solution of N-[methyl] N-[methoxy] 2-(*tert*-butyldimethylsilyl)oxy-2-(phenyl)acetamide (90.0 g, 294 mmol) (Tius, *et al.*, *Tetrahedron*, 56, 3339-3351 (2000)) in tetrahydrofuran (150 mL) via cannula. Stir the resulting slurry at $0-5^{\circ}\text{C}$ for 1 hour and then at room temperature for 1.5 hour. Cool the mixture to 10°C and then add saturated aqueous ammonium chloride. Stir the mixture 15 minutes and separate the layers. Extract the aqueous layer ethyl acetate (400 mL), dry the combined organic layers over sodium sulfate, and concentrate under reduced pressure. Subject the residue to silica gel chromatography, eluting with 1-10 % acetonitrile in dichloromethane containing 0.5% triethylamine to provide a 50% yield of the title compound as a white solid.
- MS(ESI): $m/z = 488.1$ ($M^{+}+1$)

The compounds of Preparations 30-31 were prepared essentially as described in Preparation 29.

Prep.	Compound	MS(ESI ⁺): $m/z =$
30	1-(isopropylsulfonyl)-2-amino-6-(α -((<i>tert</i> -butyldimethylsilyl)-oxy)- α -(4-(fluoro)phenyl)acetyl)benzimidazole	506.2 ($M^{+}+1$)
31	1-(isopropylsulfonyl)-2-amino-6-(α -((<i>tert</i> -butyldimethylsilyl)-oxy)- α -(4-(trifluoromethyl)phenyl)acetyl)benzimidazole	566.2 ($M^{+}+1$)

Preparation 32

- Alternate Synthesis of 1-(isopropylsulfonyl)-2-amino-6-(α -((*tert*-butyldimethylsilyl)oxy)- α -(phenyl)acetyl)benzimidazole

- Add *tert*-butyllithium (1.5 M solution, 5.8 mL, 8.65 mmol) slowly to a solution of O-(*tert*-butyldimethyl)silyl benzyl alcohol (1.9 g, 8.54 mmol) in 40 mL of anhydrous tetrahydrofuran at -78°C under a nitrogen atmosphere. Stir the solution for 3.5 hours, allowing the reaction to warm to -25°C . Cool to -35°C and add a solution of N-[methyl] N-[methoxy] 1-(isopropylsulfonyl)-2-aminobenzimidazole-6-carboxamide (0.7 g, 2.13 mmol) in 24 mL of anhydrous tetrahydrofuran. Stir the reaction for 1 hour while slowly warming to 0°C . Add saturated aqueous ammonium chloride and dilute with ethyl acetate. Extract the aqueous layer with ethyl acetate, wash the combined organic layers sequentially with water and saturated aqueous sodium chloride, dry over sodium sulfate and concentrate under reduced pressure. Subject the residue to silica gel chromatography,

eluting with 5:1 dichloromethane:acetonitrile to provide 730 mg (70%) of the title compound.

MS(ESI): $m/z = 488.1$ ($M^+ + 1$)

Preparation 33

5 1-(isopropylsulfonyl)-2-amino-6-(α -(tert-butyldimethylsilyl)oxy)- α -(3-(trifluoromethyl)phenyl)acetyl)benzimidazole

Beginning with O-(tert-butyldimethyl)silyl 3-(trifluoromethyl)benzyl alcohol, the title compound may be prepared in 83% yield essentially as described in Preparation 32.

MS(ESI): $m/z = 556.2$ ($M^+ + 1$)

10

Preparation 34

1-(benzyloxycarbonyl)-4-formylpiperidine

Add diisobutyl aluminum hydride (1 M in toluene, 30 mL, 30 mmol) over 5 minutes to a solution of 1-(benzyloxycarbonyl)-4-(ethoxycarbonyl)piperidine (7 g, 24 mmol) in anhydrous dichloromethane (150 mL) at -78°C under a nitrogen atmosphere. Stir the reaction mixture at this temperature for 30 minutes and then add 10% aqueous sodium tartarate (100 mL) followed by dichloromethane. Stir the reaction mixture at room temperature over night. Separate the phases and extract the aqueous phase with dichloromethane. Wash the combined organic phases sequentially with 10% aqueous sodium tartarate, water, and saturated aqueous sodium chloride. Dry over sodium sulfate and concentrate under reduced pressure. Subject the residue to silica gel chromatography, eluting with 3:1 hexanes:ethyl acetate to provide 3.15 gm (53%) of the title compound.

Preparation 35

1-(tert-butoxycarbonyl)-4-formylpiperidine

Beginning with 1-(tert-butoxycarbonyl)-4-(ethoxycarbonyl)piperidine, the title compound may be prepared essentially as described in Preparation 34.

Preparation 36

20 2-Chloro-6-iodo-1-(propane-2-sulfonyl)-1H-benzoimidazole

Add 1-(isopropylsulfonyl)-2-amino-6-iodobenzoimidazole (0.20 g, 0.55 mmol) in three portions over 5 minutes to a suspension of copper(II) chloride (0.089 mg, 0.66 mmol) and tert-butylnitrite (0.085 g, 0.1 mL, 0.82 mmol) in 2 mL acetonitrile at 65°C . After 30 minutes pour the resulting green solution into water and extract the aqueous layer with ethyl acetate (3 X 25 mL). Wash the combined organic phases sequentially with water (2 X 15 mL) and saturated aqueous sodium chloride (15 mL), dry over sodium sulfate, filter and concentrate under reduced pressure to provide the title compound (0.18 g, 85%).

EXAMPLE 1

2-(thien-2-yl)-4-(1-isopropylsulfonyl-2-aminobenzimidazol-6-yl)-5-phenylimidazole

Add thiophene-2-carboxaldehyde (3.16 mL, 33.8 mmol) to a stirring mixture of 1-(isopropylsulfonyl)-2-amino-6-(α -((*tert*-butyldimethylsilyl)oxy)- α -(phenyl)acetyl)-benzimidazole (15.0 g, 30.8 mmol), copper(II) acetate (11.2 g, 61.5 mmol), and ammonium acetate (23.7 g, 308 mmol) in acetic acid (300 mL). Heat the mixture at 95-100 °C and stir vigorously for 2 hours. Cool the mixture to 15°C, pour into a mixture of 750 mL saturated aqueous ammonium chloride and 250 mL concentrated ammonium hydroxide. Adjust the mixture to pH 10 with ammonium hydroxide precooled to 5 °C and then add 4 L 4:1 ethyl acetate:methanol. Separate the layers and wash the organic layer with saturated aqueous ammonium chloride (500 mL), dry over magnesium sulfate and concentrate under reduced pressure. Subject the residue to silica gel chromatography eluting with dichloromethane containing from 15-50% acetonitrile and 0.5% triethylamine. Suspend the recovered material in ethanol (75 mL), warm to 55-60 °C for 30 minutes, cool to -10 °C for 30 minutes, filter, wash sequentially with cold ethanol followed by diethyl ether. Dry under reduced pressure to provide the title compound in 40% yield as a dark yellow powder.

m.p. = 220 °C (dec.)

MS(ES⁺): m/z = 464.1 (M⁺+H)

The compounds of EXAMPLES 2-23 may be prepared essentially as described in EXAMPLE 1.

EXAMPLE	Compound	MS(ES ⁺): m/z
2	2-(thien-2-yl)-4-(1-isopropylsulfonyl-2-aminobenzimidazol-6-yl)-5-(4-fluorophenyl)imidazole	480.1 (M ⁺ +H)
3	2-(thien-2-yl)-4-(1-isopropylsulfonyl-2-aminobenzimidazol-6-yl)-5-(3-(trifluoromethyl)phenyl)imidazole	532.0 (M ⁺ +H)
4	2-(thien-2-yl)-4-(1-isopropylsulfonyl-2-aminobenzimidazol-6-yl)-5-(4-(trifluoromethyl)phenyl)imidazole	532.1 (M ⁺ +H)
5	2-(5-nitrothien-2-yl)-4-(1-isopropylsulfonyl-2-aminobenzimidazol-6-yl)-5-phenylimidazole	507.1 (M ⁺ +H)
6	4-(1-isopropylsulfonyl-2-aminobenzimidazol-6-yl)-5-phenylimidazole	382.2 (M ⁺ +H)
7	4-(1-isopropylsulfonyl-2-aminobenzimidazol-6-yl)-5-(4-fluorophenyl)imidazole	400.1 (M ⁺ +H)
8	4-(1-isopropylsulfonyl-2-aminobenzimidazol-6-yl)-5-(3-(trifluoromethyl)phenyl)imidazole	450.2 (M ⁺ +H)
9	2-(phenyl)-4-(1-isopropylsulfonyl-2-aminobenzimidazol-6-yl)-5-phenylimidazole	458.5 (M ⁺ +H)
10	2-(2-chlorophenyl)-4-(1-isopropylsulfonyl-2-aminobenzimidazol-6-yl)-5-phenylimidazole	492.0 (M ⁺ +H)
11	2-(3-chlorophenyl)-4-(1-isopropylsulfonyl-2-aminobenzimidazol-6-yl)-5-phenylimidazole	492.0 (M ⁺ +H)

12	2-(4-chlorophenyl)-4-(1-isopropylsulfonyl-2-aminobenzimidazol-6-yl)-5-phenylimidazole	492.0 (M ⁺ +H)
13	2-(4-methoxyphenyl)-4-(1-isopropylsulfonyl-2-aminobenzimidazol-6-yl)-5-phenylimidazole	487.8 (M ⁺ +H)
14	2-(4-nitrophenyl)-4-(1-isopropylsulfonyl-2-aminobenzimidazol-6-yl)-5-phenylimidazole	502.8 (M ⁺ +H)
15	2-(4-(dimethylamino)phenyl)-4-(1-isopropylsulfonyl-2-aminobenzimidazol-6-yl)-5-phenylimidazole	501.5 (M ⁺ +H)
16	2-(2,6-(difluoro)phenyl)-4-(1-isopropylsulfonyl-2-aminobenzimidazol-6-yl)-5-phenylimidazole	493.8 (M ⁺ +H)
17	2-(pyridin-4-yl)-4-(1-isopropylsulfonyl-2-aminobenzimidazol-6-yl)-5-phenylimidazole	459.1 (M ⁺ +H)
18	2-(thiazol-2-yl)-4-(1-isopropylsulfonyl-2-aminobenzimidazol-6-yl)-5-phenylimidazole	464.9 (M ⁺ +H)
19	2-(1-(ethoxycarbonyl)ethen-2-yl)-4-(1-isopropylsulfonyl-2-aminobenzimidazol-6-yl)-5-phenylimidazole	480.4 (M ⁺ +H)
20	2-(1-(<i>tert</i> -butoxycarbonyl)piperidin-4-yl)-4-(1-isopropylsulfonyl-2-aminobenzimidazol-6-yl)-5-phenylimidazole	565.3 (M ⁺ +H)
21	2-(1-(<i>tert</i> -butoxycarbonyl)piperidin-4-yl)-4-(1-isopropylsulfonyl-2-aminobenzimidazol-6-yl)-5-(4-(fluoro)phen-yl)imidazole	583.2 (M ⁺ +H)
22	2-(1-(benzyloxycarbonyl)piperidin-4-yl)-4-(1-isopropylsulfonyl-2-aminobenzimidazol-6-yl)-5-phenylimidazole	599.2 (M ⁺ +H)
23	2-(4-(2-(piperidin-4-yl)ethoxy)phenyl)-4-(1-isopropylsulfonyl-2-aminobenzimidazol-6-yl)-5-phenylimidazole trifluoroacetate	585.3 (M ⁺ +H)

EXAMPLE 24

1-(1-(*tert*-butoxycarbonyl)piperidin-4-yl)-4-phenyl-5-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)imidazole

- 5 Add *tert*-butylamine (0.125 g, 1.7 mmol) to a solution of N-[1-(ethoxycarbonyl)-piperidin-4-yl] (1-(isopropylsulfonyl)-2-amino-6-formylbenzimidazole)imine (0.36 g, 0.86 mmol) and α -(*p*-toluenesulfonyl)benzylisocyanide (0.463 g, 1.7 mmol) in methanol (10 mL). Heat the reaction mixture to reflux and stir over night. Cool to room temperature, concentrate under reduced pressure, and partition the residue between
- 10 dichloromethane (50 mL) and water (50 mL). Separate the layers, wash the organic layer with saturated aqueous sodium chloride (2 x 15 mL), dry over sodium sulfate, and concentrate under reduced pressure. Subject the residue to silica gel chromatography, eluting with 9:1 ethyl acetate:hexanes provide 0.130 g (28%) of the title compound. MS(ES⁺): m/z = 537.2 (M+H⁺).

- 15 Exact Mass: m/z: calculated for: C₁₆H₁₅N₃O₂S: 537.2284; found: 537.2283.

The compounds of EXAMPLES 25-56 may be prepared essentially as described in EXAMPLE 24.

EXAMPLE	Compound	MS(ES ⁺): m/z
---------	----------	---------------------------

25	1-(1-(<u>tert</u> -butoxycarbonyl)piperidin-4-yl)-4-(4-(fluoro)-phenyl)-5-(1-(isopropylsulfonyl)-2-amino-benzimidazol-6-yl)imidazole	555.1 (M ⁺ +H)
26	1-(1-(benzyl)piperidin-4-yl)-4-phenyl-5-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)imidazole	554.9 (M ⁺ +H)
27	1-(1-(benzyl)piperidin-4-yl)-4-(4-(fluoro)phenyl)-5-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)imidazole	572.8 (M ⁺ +H)
28	1-methyl-4-phenyl-5-(1-(isopropylsulfonyl)-2-amino-benzimidazol-6-yl)imidazole	396.0 (M ⁺ +H)
29	1-(2-(hydroxy)eth-1-yl)-4-phenyl-5-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)imidazole	425.9 (M ⁺ +H)
30	1-(2-(methoxy)eth-1-yl)-4-phenyl-5-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)imidazole	440.6 (M ⁺ +H)
31	1-(2-(N-[<u>tert</u> -butoxycarbonyl]amino)eth-1-yl)-4-phenyl-5-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)imidazole	524.9 (M ⁺ +H)
32	1-(cyclopropylmethyl)-4-phenyl-5-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)imidazole	436.1 (M ⁺ +H)
33	1-(cyclopropylmethyl)-4-(4-(fluoro)phenyl)-5-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)imidazole	455.1 (M ⁺ +H)
34	1-(4-(fluoro)benzyl)-4-phenyl-5-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)imidazole	489.9 (M ⁺ +H)
35	1-(2,4-(difluoro)benzyl)-4-phenyl-5-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)imidazole	507.9 (M ⁺ +H)
36	1-((pyridin-2-yl)methyl)-4-phenyl-5-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)imidazole	472.9 (M ⁺ +H)
37	1-((pyridin-3-yl)methyl)-4-phenyl-5-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)imidazole	472.9 (M ⁺ +H)
38	1-((pyridin-4-yl)methyl)-4-phenyl-5-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)imidazole	473.0 (M ⁺ +H)
39	1-(3-(phenyl)prop-1-yl)-4-phenyl-5-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)imidazole	499.2 (M ⁺ +H)
40	1-(2-(morpholin-4-yl)eth-1-yl)-4-phenyl-5-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)imidazole	494.8 (M ⁺ +H)
41	1-(2-(morpholin-4-yl)eth-1-yl)-4-(4-(fluoro)phenyl)-5-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)imidazole	513.0 (M ⁺ +H)
42	1-(3-(morpholin-4-yl)prop-1-yl)-4-phenyl-5-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)imidazole	509.1 (M ⁺ +H)
43	1-cyclohexyl-4-phenyl-5-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)imidazole	464.0 (M ⁺ +H)
44	1-(<u>trans</u> -4-hydroxycyclohex-1-yl)-4-phenyl-5-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)imidazole	479.9 (M ⁺ +H)
45	1-(<u>trans</u> -4-hydroxycyclohex-1-yl)-4-(4-(fluoro)phenyl)-	498.0 (M ⁺ +H)

	5-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)-imidazole	
46	1-(<u>trans</u> -4-hydroxycyclohex-1-yl)-4-(thien-3-yl)-5-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)imidazole	486.0 (M ⁺ +H)
47	1-(4-(N-[<u>tert</u> -butoxycarbonyl]amino)cyclohex-1-yl)-4-phenyl-5-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)imidazole	578.9 (M ⁺ +H)
48	1-(1,4-dioxaspiro[4.5]dec-8-yl)-4-phenyl-5-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)imidazole	522.2 (M ⁺ +H)
49	1-(tetrahydropyran-4-yl)-4-phenyl-5-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)imidazole	465.9 (M ⁺ +H)
50	1-(2,2,6,6-tetramethylpiperidin-4-yl)-4-phenyl-5-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)imidazole	521.0 (M ⁺ +H)
51	1-(R-(3-hydroxyprop-2-yl))-4-phenyl-5-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)imidazole	440.0 (M ⁺ +H)
52	1-(S-(3-hydroxyprop-2-yl))-4-phenyl-5-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)imidazole	440.0 (M ⁺ +H)
53	1-(S-(3-hydroxyprop-2-yl))-4-(4-fluorophenyl)-5-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)imidazole	458.4 (M ⁺ +H)
54	1-(isopropyl)-4-phenyl-5-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)imidazole	424.4 (M ⁺ +H)
55	1-(isopropyl)-4-(4-fluorophenyl)-5-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)imidazole	442.4 (M ⁺ +H)
56	1-(2-(methoxycarbonyl)eth-1-yl)-4-phenyl-5-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)imidazole	468.0 (M ⁺ +H)

EXAMPLE 57

2-methyl-4-phenyl-5-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)thiazole

2-methyl-4-phenylthiazole

- 5 Add thioacetamide (0.09 g, 1.2 mmol) to a solution of 2-bromoacetophenone (0.2 g, 1.0 mmol) in 30 mL dioxane. Stir at room temperature for 4 hours, dilute with ethyl acetate, wash sequentially with aqueous sodium carbonate (3 x 15 mL) and water (3 x 20 mL). Dry the organic phase over sodium sulfate, concentrate under reduced pressure, and subject the residue to silica gel chromatography, eluting with hexane containing 10% ethyl acetate to provide the desired compound in 78% yield.
- 10 MS(ES): m/z = 176.1 (M⁺+1)

2-methyl-4-phenyl-5-(tributylstannyl)thiazole

- 15 Add *n*-butyllithium (0.46 mL, 0.74 mmol, 1.6 M in tetrahydrofuran) to a solution of 2-methyl-4-phenylthiazole (0.13 g, 0.74 mmol) in tetrahydrofuran (7 mL) cooled to -78°C under a nitrogen atmosphere. Stir at -78°C for 45 minutes, add tributyltin chloride (0.2 mL, 0.74 mmol), and stir for 2 hours as the reaction mixture warms to room temperature. Add aqueous ammonium chloride and then partition the mixture between

ethyl acetate and water. Extract the aqueous phase with ethyl acetate. Wash the combined organic layers sequentially with water and saturated aqueous sodium chloride, dry over sodium sulfate, and concentrate under reduced pressure. Subject the residue to silica gel chromatography, eluting with hexane containing 10% ethyl acetate to provide the desired compound in 68% yield.

MS(ES): $m/z = 466.1$ ($M^+ + 1$)

Coupling

Stir a mixture of 2-methyl-4-phenyl-5-(tributylstannyl)thiazole (0.1 g, 0.21 mmol), 1-(isopropylsulfonyl)-2-amino-6-iodobenzimidazole (0.07 g, 0.21 mmol), and (acetonitrile)palladium(II) chloride (0.021 mmol) in dry dimethylformamide (2 mL) at 100°C for 4 hours under a nitrogen atmosphere. Cool to room temperature and dilute with ethyl acetate (20 mL). Wash sequentially with water (3 x 5 mL) and saturated aqueous sodium chloride (3 x 5 mL), dry over sodium sulfate, and concentrate under reduced pressure. Subject the residue to silica gel chromatography, eluting with 7:1 dichloromethane:acetonitrile to provide the title compound as a white solid in 2% yield.

MS(ES): $m/z = 413.0$ ($M^+ + 1$)

EXAMPLE 58

2,4-diphenyl-5-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)thiazole

Beginning with thiobenzamide and 2-bromoacetophenone, the title compound may be prepared in 12% yield essentially as described in EXAMPLE 50.

MS(ES): $m/z = 474.8$ ($M^+ + 1$)

EXAMPLE 59

2-(2,6-difluorophenyl)-4-(2-aminobenzimidazol-6-yl)-5-phenylimidazole

Stir a mixture of 2-(2,6-difluorophenyl)-4-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)-5-phenylimidazole (0.07 g, 0.142 mmol) and 1.42 mL 1N sodium hydroxide in 1:1 water:acetonitrile at 60°C for 1 hour. Cool the mixture to room temperature and dilute with water and ethyl acetate. Extract the aqueous phase with ethyl acetate (3 times). Wash the combined organic phases sequentially with water and saturated aqueous sodium chloride, dry over sodium sulfate, and concentrate under reduced pressure. Subject the residue to silica gel chromatography, eluting with 2:1 dichloromethane:methanol to provide the title compound in 93% yield.

MS(ES): $m/z = 388.0$ ($M^+ + 1$)

The compounds of EXAMPLES 60-61 may be prepared essentially as described in EXAMPLE 59.

EXAMPLE	Compound	MS(ESI ⁺): m/z
60	4-(2-aminobenzimidazol-6-yl)-5-phenylimidazole	276.0 (M ⁺ +H)
61	2-(thien-2-yl)-4-(2-aminobenzimidazol-6-yl)-5-phenylimidazole	358.8 (M ⁺ +H)

EXAMPLE 62

2-(4-aminophenyl)-4-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)-5-phenylimidazole

Purge a suspension of 2-(4-nitrophenyl)-4-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)-5-phenylimidazole (0.149 g, 0.3 mmol) and 10% palladium on carbon (0.03 mmol) in methanol with hydrogen for 10 minutes and then stir under a hydrogen atmosphere for 6 hours. Filter through a bed of CELITE™ and concentrate the residue under reduced pressure. Subject the residue to silica gel chromatography, eluting with 4% methanol in dichloromethane to provide the title compound in 28% yield.

MS(ES): $m/z = 473.0$ ($M^+ + 1$)

EXAMPLE 63

2-(2-aminothien-5-yl)-4-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)-5-phenylimidazole

Beginning with 2-(2-nitrothien-5-yl)-4-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)-5-phenylimidazole, the title compound may be prepared in 22% yield essentially as described in EXAMPLE 56.

MS(ES): $m/z = 479.0$ ($M^+ + 1$)

EXAMPLE 64

1-methyl-2-(2,6-difluorophenyl)-4-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)-5-phenylimidazole and 1-methyl-2-(2,6-difluorophenyl)-4-phenyl-5-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)imidazole

Add cesium carbonate (0.134 mmol) and methyl iodide (0.134 mmol) to a solution of 2-(2,6-difluorophenyl)-4-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)-5-phenylimidazole (0.12 mmol) in dry dimethylformamide (2.5 mL) at 0°C. Stir the mixture at room temperature for 16 hours, dilute with water and ethyl acetate, and separate the layers. Extract the aqueous phase with ethyl acetate (3 times). Wash the combined organic phases sequentially with cold water (5 times) and saturated aqueous sodium chloride. dry over sodium sulfate, and concentrate under reduced pressure. Subject the residue to silica gel chromatography. Dissolve the isomer mixture in dichloromethane and subject this mixture to preparative HPLC (Kromasil Si60, 7 μ m, 20 x 250 mm ID) eluting with dichloromethane containing 4% methanol (10 mL/min) to provide 1-methyl-2-(2,6-difluorophenyl)-4-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)-5-phenylimidazole (11.1 min) in 22% yield (MS(ES): $m/z = 508.2$ ($M^+ + 1$)) and 1-methyl-2-(2,6-difluorophenyl)-4-phenyl-5-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)imidazole (16.1 min) in 33% yield (MS(ES): $m/z = 508.2$ ($M^+ + 1$)).

EXAMPLE 65

1-methyl-2-(thien-2-yl)-4-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)-5-phenylimidazole and 1-methyl-2-(thien-2-yl)-4-phenyl-5-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)imidazole

Beginning with 2-(thien-2-yl)-4-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)-5-phenylimidazole, 1-methyl-2-(thien-2-yl)-4-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)-5-phenylimidazole and 1-methyl-2-(thien-2-yl)-4-phenyl-5-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)imidazole may be prepared essentially as described in EXAMPLE 57.

MS(ES): $m/z = 478.2$ ($M^+ + 1$)

EXAMPLE 66

2-(piperidin-4-yl)-4-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)-5-phenylimidazole

Vigorously stir a mixture of 2-(1-(benzyloxycarbonyl)piperidin-4-yl)-4-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)-5-phenylimidazole (0.74 g, 1.24 mmol), ammonium formate (4.94 mmol), and 10% palladium on carbon (0.12 mmol) in 30 mL absolute ethanol at reflux for 5 hours. Cool the reaction mixture to room temperature, filter through a bed of CELITE™, and concentrate the filtrate under reduced pressure. Subject the residue to silica gel chromatography, eluting with 19:1 dichloromethane:methanol to provide the title compound:

MS(ES): $m/z = 465.2$ ($M^+ + 1$)

EXAMPLE 67

2-(piperidin-4-yl)-4-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)-5-(4-fluorophenyl)imidazole di-trifluoroacetate

Add hydrogen chloride in ethyl acetate to a solution of 2-(1-(~~tert~~-butoxycarbonyl)-piperidin-4-yl)-4-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)-5-(4-fluorophenyl)-imidazole (0.05 mmol) in ethyl acetate (2 mL) and stir the mixture at room temperature over night. Filter the resulting suspension and wash with diethyl ether to provide the title compound in 25% yield. Dissolve the solid in 1:1 dimethylsulfoxide:acetonitrile and subject to HPLC (YMC C18, 5 μ m, 20 x 50 mm ID) eluting with a gradient of water+0.05% trifluoroacetic acid:acetonitrile+0.05% trifluoroacetic acid from 90:10 to 45:55 in 15 minutes (9 mL/min) to provide the title compound 25%, 9.33 min).

MS(ES): $m/z = 483.2$ ($M^+ + 1$)

EXAMPLE 68

1-(piperidin-4-yl)-4-phenyl-5-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)imidazole

Heat a mixture of 1-(1-(ethoxycarbonyl)piperidin-4-yl)-4-phenyl-5-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)imidazole (55 mg) in concentrated hydrochloric acid at reflux for 24 hours. Cool the mixture to room temperature, add 5N sodium hydroxide until the mixture is basic, and extract with dichloromethane. Concentrate the organic phase under reduced pressure and subject the residue to silica gel chromatography, eluting with dichloromethane followed by 1:1 dichloromethane:methanol to provide 20 mg (43%) of the title compound.

MS(ES): $m/z = 465.0$ ($M^+ + 1$)

EXAMPLE 69

1-(piperidin-4-yl)-4-(4-fluorophenyl)-5-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)imidazole

Beginning with 1-(1-(ethoxycarbonyl)piperidin-4-yl)-4-(4-fluorophenyl)-5-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)imidazole, the title compound may be prepared essentially as described in EXAMPLE 68.

MS(ES): $m/z = 483.0$ ($M^+ + 1$)

EXAMPLE 70

2-(1-(ethyl)piperidin-4-yl)-4-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)-5-phenylimidazole

Stir a mixture of 2-(piperidin-4-yl)-4-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)-5-phenylimidazole (0.574 g, 1.23 mmol), triethylamine (3.1 mmol), and iodoethane (1.54 mmol) in anhydrous dimethylformamide (5 mL) at room temperature for 6 hours. Partition the mixture between ethyl acetate and water. Extract the aqueous layer with ethyl acetate (3 times). Wash the combined organic layers sequentially with cold water (5 times) and saturated aqueous sodium chloride, dry over sodium sulfate, and concentrate under reduced pressure. Subject the residue to silica gel chromatography to provide the title compound in 76% yield.

MS(ES): $m/z = 493.2$ ($M^+ + 1$)

The compounds of EXAMPLES 71-74 may be prepared essentially as described in EXAMPLE 70.

EXAMPLE	Compound	MS(ESI ⁺): m/z
71	2-(1-(methyl)piperidin-4-yl)-4-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)-5-phenylimidazole	479.1 ($M^+ + H$)
72	2-(1-(3,3,3-trifluoroprop-1-yl)piperidin-4-yl)-4-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)-5-	561.3 ($M^+ + H$)

	phenylimidazole	
73	2-(1-(2-hydroxyeth-1-yl)piperidin-4-yl)-4-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)-5-phenylimidazole	509.2 (M ⁺ +H)
74	2-(1-(benzyl)piperidin-4-yl)-4-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)-5-phenylimidazole	555.2 (M ⁺ +H)

EXAMPLE 75

1-(1-(methyl)piperidin-4-yl)-4-phenyl-5-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)-imidazole

- 5 Add aqueous formaldehyde (37% w/w, 0.15 mmol) to a solution of 1-(piperidin-4-yl)-4-phenyl-5-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)imidazole (75 mg) in methanol (10 mL). Stir the mixture at room temperature for 30 minutes, then cool to 0°C. Add acetic acid (0.3 mL) followed by sodium cyanoborohydride (18 mg) and stir over
- 10 night at room temperature. Concentrate the mixture under reduced pressure and then dissolve residue in ethyl acetate. Wash the solution twice with 1N sodium hydroxide and concentrate the organic phase under reduced pressure to provide 60 mg (79%) of the title compound.

MS(ES): $m/z = 479.6 (M^+ + 1)$

The compounds of EXAMPLES 76-77 may be prepared essentially as described in EXAMPLE 75.

EXAMPLE	Compound	MS(ESI ⁺): m/z
76	1-(1-(methyl)piperidin-4-yl)-4-(4-fluorophenyl)-5-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)imidazole	497.6 (M ⁺ +H)
77	1-(1-(isopropyl)piperidin-4-yl)-4-phenyl-5-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)imidazole	507.6 (M ⁺ +H)

EXAMPLE 78

- 5 1-(cyclohexan-1-on-4-yl)-4-phenyl-5-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)-imidazole

Stir a solution of 1-(1,4-dioxaspiro[4.5]dec-8-yl)-4-phenyl-5-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)imidazole (0.05 g, 0.1 mmol) in 3N hydrochloric acid (5 mL) for 3 days at room temperature. Add 5N sodium hydroxide to neutralize the mixture and extract with dichloromethane (3 x 10 mL). Dry the combined organic phases over sodium sulfate and concentrate under reduced pressure to provide 0.038 g (83%) of the title compound.

MS(ES): m/z = 478.2 (M⁺+1)

EXAMPLE 79

- 15 1-(4-hydroxycyclohex-1-yl)-4-phenyl-5-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)-imidazole

Add a solution of sodium borohydride (0.28 g) in methanol (5 mL) to a solution of 1-(cyclohexan-1-on-4-yl)-4-phenyl-5-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)-imidazole (0.35 g, 0.7 mmol) in 10 mL tetrahydrofuran and 10 mL methanol. Stir the reaction mixture for 30 minutes at room temperature, dilute with water (50 mL), and extract with ethyl acetate (2 x 15 mL). Wash the combined organic extracts with saturated aqueous sodium chloride, dry over sodium sulfate, and concentrate under reduced pressure to provide 0.345 g (98%) of the title compound.

- 25 MS(ES): m/z = 480.2 (M⁺+1)

EXAMPLE 80

1-(4-aminocyclohex-1-yl)-4-phenyl-5-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)-imidazole hydrochloride

5 Stir a solution of 1-(4-(N-[tert-butoxycarbonyl]amino)cyclohex-1-yl)-4-phenyl-5-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)imidazole (0.14 g, 0.2 mmol) in 1M hydrogen chloride in acetic acid (5 mL) at room temperature for 1 hour. Filter the suspension and dry the solid to provide 0.017 g (15%) of the title compound.
MS(ES): $m/z = 479.0$ ($M^+ + 1$)

10

EXAMPLE 81

1-(2,4-difluorobenzyl)-4-phenyl-5-(1-(isopropylsulfonyl)-2-chlorobenzimidazol-6-yl)-imidazole

15 Add 1-(2,4-difluorobenzyl)-4-phenyl-5-(1-(isopropylsulfonyl)-2-aminobenzimidazol-6-yl)imidazole (0.15 g, 0.29 mmol) in three portions over 5 minutes to a suspension of copper(II) chloride (0.049 g, 0.29 mMol) and tert-butylnitrite (0.049 g, 0.05 mL, 0.44 mmol) in 1 mL acetonitrile at 65°C. Add 0.1 mL ethylenediamine, pour the reaction mixture into water, and extract with ethyl acetate (3 x 25 mL). Wash the combined organic phases sequentially with water (2 x 15 mL) followed by saturated aqueous sodium chloride (15 mL), dry over sodium sulfate, and concentrate under reduced
20 pressure. Subject the residue to silica gel chromatography, eluting with a gradient of hexane containing from 25-50% ethyl acetate to provide the title compound (0.08 g, 52%).

EXAMPLE 82

25 1-(2,4-difluorobenzyl)-4-phenyl-5-(1-(isopropylsulfonyl)-2-(benzylamino)benzimidazol-6-yl)imidazole

Add benzylamine (0.10 g, 0.19 mmol) to a solution of 1-(2,4-difluorobenzyl)-4-phenyl-5-(1-(isopropylsulfonyl)-2-chlorobenzimidazol-6-yl)-imidazole (0.061 g, 0.57 mmol) in 1 mL tetrahydrofuran. After 24 hours concentrate the reaction mixture under
30 reduced pressure. Subject the residue to silica gel chromatography, eluting with hexane containing 25% ethyl acetate to provide the title compound (0.069 g, 61%).
MS(ES): $m/z = 598.0$ ($M^+ + 1$)

EXAMPLE 83

35 1-(2,4-difluorobenzyl)-4-phenyl-5-(2-(benzylamino)benzimidazol-6-yl)imidazole

Add 0.1 mL 2N sodium hydroxide to a solution of 1-(2,4-difluorobenzyl)-4-phenyl-5-(1-(isopropylsulfonyl)-2-(benzylamino)benzimidazol-6-yl)imidazole (0.03 g,

0.05 mmol) in 0.5 mL tetrahydrofuran. Heat the solution to 60°C. After 24 hours cool the mixture to room temperature, add 5 mL saturated aqueous ammonium chloride, and extract with ethyl acetate (3 x 10 mL). Combine the organic phases and concentrate under reduced pressure. Subject the residue to silica gel chromatography, eluting with 1:1 ethyl acetate:hexane to provide the title compound (0.011 g, 45%).

MS(ES): $m/z = 492.0$ ($M^+ + 1$)

The ability of the compounds of the present invention to inhibit p38 kinase is demonstrated by standard assays well known to the skilled artisan, and are briefly described in the following paragraphs.

Inhibition of p38 Kinase

Standard Solution Preparations

The kinase buffer solution is prepared by combining 2.5 mL 1M Tris-HCl (pH 7.5), 0.1 mL 1M dithiothreitol, 1.0 mL 1M magnesium chloride, and 300 μ L 1% Triton X-100 and dilute to 100 mL with water. Combine 84 mL of this kinase buffer solution with 16 mL dimethylsulfoxide to prepare the 16% DMSO solution.

The 200 μ M ATP solution is prepared by adding 102.6 μ L 10 mM aqueous ATP, 25 μ L 33 P-ATP, and 163.5 μ L of 4 mM aqueous Epidermal Growth Factor Peptide 661-681 (Biomol, Catalog #P-121) in 5 mL kinase buffer solution.

The p38 kinase enzyme solution is prepared by dissolving 9.5 μ L concentrated enzyme solution (250 ng p38 enzyme/ μ L kinase buffer solution) in 1536 μ L kinase buffer solution.

Sample Preparation

Prepare an 80 μ M solution of each test compound and control compound by dissolving 2 μ L of a 10mM stock solution of the respective compounds in dimethylsulfoxide in 248 μ L of the 16% DMSO solution in a Costar 96-well microtiter plate. Place the plate onto the Tecan Genesis automated liquid handler for 1:3 serial dilutions.

Assay

Place 10 μ L of serially diluted compound with Beckman Multimek 96-well automated liquid handler to the assay plate. Add 20 μ L of 200 μ M ATP solution with Titertek Multidrop 8-channel liquid handler. Transfer 10 μ L of p38 kinase enzyme solution to the assay plate using the Multimek. Allow the mixture to react for 40 minutes at 30°C and then stop reaction by adding 60 μ L of freshly prepared 5% glacial acetic acid

with Multidrop. Transfer 80 μ L of this solution to an "MAPH" plate using the Multimek. Allow the plates to set for 30 minutes at room temperature and then wash/aspirate on the Titertek MAP extractor with freshly prepared 0.5% glacial acetic acid (1 x 300 μ L, 2 x 200 μ L). Blot wells and add 100 μ L MicroScint-20 scintillation fluid (Packard Bioscience) with the Multidrop. Allow plates to sit for 30 minutes and count on a PE/Wallac Microbeta Trilux scintillation counter for 33 P-isotope.

All exemplified compounds were initially tested at 10 concentrations (20 μ M – 1 nM using 1:3 serial dilutions). Compounds with IC_{50} values less than 25 nM were re-tested at a starting concentration of 2 μ M to 0.1 nM (1:3 serial dilutions). IC_{50} values were calculated (IDBS ActivityBase software) for each compound using non-linear regression. All exemplified compounds were tested essentially as described above and were found to inhibit the p38 kinase enzyme with an IC_{50} of at least 5 μ M.

Inhibition of TNF- α *in vitro*

15 Mouse Peritoneal Macrophages

Inject 1 mL thioglycolate broth (5.0 g yeast extract, 15.0 g casitone or trypticase, 5.0 g dextrose, 2.5 g sodium chloride, 0.75 g L-cystine, 0.5 g sodium thioglycolate, 1.0 mg resazurin, and 0.75 g agar in 1.0 L distilled water) into the peritoneal cavity of Balb/C female mice. At day 4 or 5 post-injection the mice are sacrificed and then injected i.p. with 4 mL RPMI-1640 medium (BioWhittaker) and the peritoneal macrophages are withdrawn by syringe.

Cytokine Production

Count mouse peritoneal microphages with a hemocytometer and adjust to 5×10^5 cells/well in 96-well plates in RPMI-1640 medium with 10% fetal bovine serum. Plate 200 μ L/well in 96-well plates and allow the cells to settle and adhere to the bottom of the well for at least 3 hours. Pre-treat cells with test compound or standard p38 kinase inhibitor using a series of 8 concentrations for 1 hour at 37°C (20 μ L/well). Treat cells with a mixture of 50 ng/mL lipopolysaccharide (LPS) and 10 U/mL interferon- γ for 18 hours at 37°C (20 μ L/well). Harvest conditioned media and assay for TNF- α production using the Luminex procedure.

TNF- α /Luminex Detection Assay (Bio-Rad Bio-Plex Kit – Catalog #171-G12221)

Reconstitute the lyophilized premixed TNF- α standard (1 standard tube/ two 96-well plates) with 50 μ L sterile water (500,000 pg/mL). Gently vortex for 5 seconds, incubate on ice for 30 minutes, and vortex for 5 seconds before use. Label a set of twelve 1.5 ml tubes with #1-thru #12 and then add the amounts of cell media shown below to the appropriate tubes (standard concentrations are as follows: 50,000; 25,000; 12,500; 6,250;

3,125; 1,562.5; 781.3; 390.6; 195.3; 97.7; 48.8; and 24.4 pg/mL). Vortex the premixed anti-cytokine conjugated beads (25X) vigorously for 30 seconds. Dilute the anti-cytokine conjugated beads to a 1X concentration using 1X Bio-Plex Assay Buffer. For every plate, add 240 μ L of the pre-mixed beads to 5760 μ L of Bio-Plex Assay Buffer. Block a

5 Millipore 96-well filter plate with 100 μ L/well of blocking buffer. Filter through the blocking buffer using a Millipore filtration system. Towel dry. Perform 2 washes on the filter plate with 100 μ L/well of Bio-Plex Assay Buffer and towel dry. Vortex the 1X anti-cytokine conjugated beads for 15 seconds and add 50 μ L to each well. Filter through and towel dry. Perform 2 washes on plates with 100 μ L/well of Bio-Plex Wash Buffer. Filter

10 thru and towel dry. Add 50 μ L of sample or standard to each sample well. Incubate for 60 seconds at room temperature on a shaker protected from light at setting 6 and then for 30 minutes at setting 3 and then place in the refrigerator overnight. Perform 3 washes with Bio-Plex Wash Buffer. Filter through and towel dry. Prepare cytokine detection antibody (~10 minutes prior to use) for every plate, add 60 μ L of the premixed cytokine

15 detection antibody stock to 5940 μ L of Bio-Plex Detection Antibody Diluent. Add 50 μ L of cytokine detection antibody and incubate for 60 seconds at room temp on a shaker protected from light at setting 6 and then for 30 minutes at setting 3. Perform 3 washes with Bio-Plex Wash Buffer. Filter through and towel dry. Prepare strept-PE (~10 minutes prior to use) for every plate, add 60 μ L to 5940 μ L of Bio-Plex Assay Buffer.

20 Add 50 μ L of Streptavidin-PE to each well and incubate for 60 seconds at room temp on a shaker protected from light at setting 6 and then for 10 minutes at setting 3. Perform 3 washes with Bio-Plex Wash Buffer. Filter through. Re-suspend the beads in 100 μ L/well of Bio-Plex Assay Buffer. Read standards and samples on Luminex machine. These intensity readings are then converted to picogram/milliliter units based on a 12-point

25 standard curve created in duplicate using a four-parameter logistic regression method (Bio-Plex Manager 2.0, Bio-Rad), and the IC_{50} calculated.

The compounds of Examples 1, 6, 16, and 17 were tested essentially as described above and suppressed TNF- α *in vitro* with an IC_{50} less than 100 nM.

30 Inhibition of TNF- α *in vivo*

Compounds are administered p.o. (100, 30, 10 and 3 mg/kg) to female Balb/c mice (5 mice/dose). After 2 hours, lipopolysaccharide (LPS, E. coli serotype 0111:B4, 5 mg/kg) is administered i.v. in the tail vein of each mouse. One hour after LPS administration the mice are asphyxiated by CO₂ inhalation and bled out via cardiac

35 puncture.

TNF- α Luminex Detection Assay (Bio-Rad Bio-Plex Kit – Catalog #171-G12221)

Reconstitute the lyophilized premixed TNF- α standard (1 standard tube/ two 96-well plates) with 50 μ L sterile water (500,000 pg/mL). Gently vortex for 5 seconds, incubate on ice for 30 minutes, and vortex for 5 seconds before use. Label a set of twelve 1.5 ml tubes with #1-thru #12 and then add the amounts of cell media shown below to the appropriate tubes (standard concentrations are as follows: 50,000; 25,000; 12,500; 6,250; 3,125; 1,562.5; 781.3; 390.6; 195.3; 97.7; 48.8; and 24.4 pg/mL). Vortex the premixed anti-cytokine conjugated beads (25X) vigorously for 30 seconds. Dilute the anti-cytokine conjugated beads to a 1X concentration using 1X Bio-Plex Assay Buffer. For every plate, add 240 μ L of the pre-mixed beads to 5760 μ L of Bio-Plex Assay Buffer. Block a Millipore 96-well filter plate with 100 μ L/well of blocking buffer. Filter through the blocking buffer using a Millipore filtration system. Towel dry. Perform 2 washes on the filter plate with 100 μ L/well of Bio-Plex Assay Buffer and towel dry. Vortex the 1X anti-cytokine conjugated beads for 15 seconds and add 50 μ L to each well. Filter through and towel dry. Perform 2 washes on plates with 100 μ L/well of Bio-Plex Wash Buffer. Filter thru and towel dry. Add 25 μ L of serum sample and 25 μ L of diluent (Bio-Rad) or 50 μ L standard to each sample well. Incubate for 60 seconds at room temperature on a shaker protected from light at setting 6 and then for 30 minutes at setting 3 and then place in the refrigerator overnight. Perform 3 washes with Bio-Plex Wash Buffer. Filter through and towel dry. Prepare cytokine detection antibody (~10 minutes prior to use) for every plate, add 60 μ L of the premixed cytokine detection antibody stock to 5940 μ L of Bio-Plex Detection Antibody Diluent. Add 50 μ L of cytokine detection antibody and incubate for 60 seconds at room temp on a shaker protected from light at setting 6 and then for 30 minutes at setting 3. Perform 3 washes with Bio-Plex Wash Buffer. Filter through and towel dry. Prepare strept-PE (~10 minutes prior to use) for every plate, add 60 μ L to 5940 μ L of Bio-Plex Assay Buffer. Add 50 μ L of Streptavidin-PE to each well and incubate for 60 seconds at room temp on a shaker protected from light at setting 6 and then for 10 minutes at setting 3. Perform 3 washes with Bio-Plex Wash Buffer. Filter through. Re-suspend the beads in 100 μ L/well of Bio-Plex Assay Buffer. Read standards and samples on Luminex machine. These intensity readings are then converted to picogram/milliliter units based on a 12-point standard curve created in duplicate using a four-parameter logistic regression method (Bio-Plex Manager 2.0, Bio-Rad), and the IC₅₀ calculated.

The compounds of Examples 1, 6, 16, and 17 were tested essentially as described above and suppressed TNF- α in vivo with an IC₅₀ less than 100 mg/kg.

Oral administration of the compounds of the present invention is preferred. However, oral administration is not the only route or even the only preferred route. For

example, transdermal administration may be very desirable for patients who are forgetful or petulant about taking oral medicine, and the intravenous route may be preferred as a matter of convenience or to avoid potential complications related to oral administration. Compounds of Formula I may also be administered by the percutaneous, intramuscular, intranasal or intrarectal route in particular circumstances. The route of administration may be varied in any way, limited by the physical properties of the drugs, the convenience of the patient and the caregiver, and other relevant circumstances (Remington's Pharmaceutical Sciences, 18th Edition, Mack Publishing Co. (1990)).

The pharmaceutical compositions are prepared in a manner well known in the pharmaceutical art. The carrier or excipient may be a solid, semi-solid, or liquid material that can serve as a vehicle or medium for the active ingredient. Suitable carriers or excipients are well known in the art. The pharmaceutical composition may be adapted for oral, inhalation, parenteral, or topical use and may be administered to the patient in the form of tablets, capsules, aerosols, inhalants, suppositories, solutions, suspensions, or the like.

The compounds of the present invention may be administered orally, for example, with an inert diluent or capsules or compressed into tablets. For the purpose of oral therapeutic administration, the compounds may be incorporated with excipients and used in the form of tablets, troches, capsules, elixirs, suspensions, syrups, wafers, chewing gums and the like. These preparations should contain at least 4% of the compound of the present invention, the active ingredient, but may be varied depending upon the particular form and may conveniently be between 4% to about 70% of the weight of the unit. The amount of the compound present in compositions is such that a suitable dosage will be obtained. Preferred compositions and preparations of the present invention may be determined by methods well known to the skilled artisan.

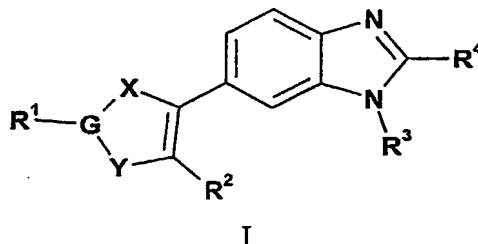
The tablets, pills, capsules, troches, and the like may also contain one or more of the following adjuvants: binders such as povidone, hydroxypropyl cellulose, microcrystalline cellulose, or gelatin; excipients or diluents such as: starch, lactose, microcrystalline cellulose or dicalcium phosphate, disintegrating agents such as: croscarmellose, crospovidone, sodium starch glycolate, corn starch and the like; lubricants such as: magnesium stearate, stearic acid, talc or hydrogenated vegetable oil; glidants such as colloidal silicon dioxide; wetting agents such as: sodium lauryl sulfate and polysorbate 80; and sweetening agents such as: sucrose, aspartame or saccharin may be added or a flavoring agent such as: peppermint, methyl salicylate or orange flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as polyethylene glycol or a fatty oil. Other dosage unit forms may contain other various materials that modify the physical form of the dosage

unit, for example, as coatings. Thus, tablets or pills may be coated with sugar, hydroxypropyl methylcellulose, polymethacrylates, or other coating agents. Syrups may contain, in addition to the present compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors. Materials used in preparing these various compositions should be pharmaceutically pure and non-toxic in the amounts used.

The compounds of Formula I are generally effective over a wide dosage range. For example, dosages per day normally fall within the range of about 0.0001 to about 30 mg/kg of body weight. In some instances dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect, and therefore the above dosage range is not intended to limit the scope of the invention in any way. It will be understood that the amount of the compound actually administered will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound or compounds administered, the age, weight, and response of the individual patient, and the severity of the patient's symptoms.

WE CLAIM:

1. A compound of Formula I:



5 where:

R¹ is hydrogen, C₁-C₄ alkyl, 1-(C₁-C₄ alkoxy-carbonyl)ethen-2-yl, phenyl optionally substituted with one or two substituents individually selected from the group consisting of halo, nitro, C₁-C₄ alkoxy, C₂-C₄ alkoxy substituted with piperidin-1-yl, and -NR⁵R⁶, pyridinyl, thiazolyl, or piperidin-4-yl optionally substituted at the 1-position with C₁-C₄ alkoxy-carbonyl or (C₁-C₄ alkylene)-R⁷;

R² is phenyl optionally substituted with halo or trifluoromethyl;

R³ is hydrogen or (C₁-C₄ alkyl)sulfonyl;

R⁴ is halo or -NR⁸R⁹

R⁵ and R⁶ are individually at each occurrence selected from hydrogen or C₁-C₄

15 alkyl;

R⁷ is hydrogen, hydroxy, trifluoromethyl, or phenyl;

R⁸ is hydrogen or C₁-C₄ alkyl;

R⁹ is hydrogen, C₁-C₄ alkyl, or benzyl;

X-G-Y is -N=C-N(R¹⁰)-, -N(R¹¹)-C=N-, or -S-C=N-;

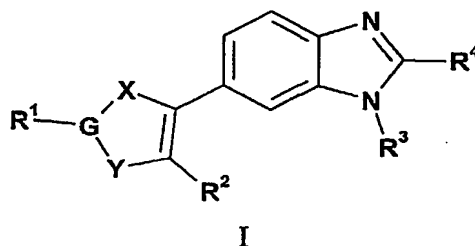
20 R¹⁰ is hydrogen or C₁-C₄ alkyl;

R¹¹ is hydrogen, cyclohex-1-yl optionally substituted in the 4-position with hydroxy, amino, N-[C₁-C₄ alkoxy-carbonyl]amino, oxo, or ethylene glycol ketal, (C₁-C₄ alkylene)-R¹², piperidin-4-yl optionally substituted at the 1-position with C₁-C₄ alkyl or C₁-C₄ alkoxy-carbonyl, or 2,2,6,6-tetramethylpiperidin-4-yl;

25 R¹² is hydrogen, hydroxy, C₁-C₄ alkoxy, C₁-C₄ alkoxy-carbonyl, N-[C₁-C₄ alkoxy-carbonyl]amino, C₃-C₆ cycloalkyl, tetrahydropyran-4-yl, morpholin-4-yl, or phenyl optionally substituted with one or two substituents individually selected from halo; provided that when X-G-Y is -N(R¹¹)-C=N-, then at least one of R¹ and R¹¹ is hydrogen or C₁-C₄ alkyl; or a pharmaceutically acceptable salt thereof.

30 2. A compound of Claim 1, where X-G-Y is either -N=C-N(R¹⁰)- or -N(R¹¹)-C=N-.

3. A compound of either of Claims 1 or 2, where R^4 is $-NH_2$.
4. A compound of Claim 3, where R^3 is isopropylsulfonyl.
5. A pharmaceutical formulation comprising a compound of Formula I:

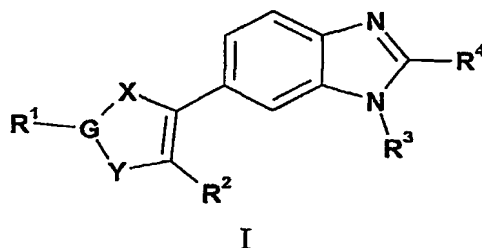


where:

- R^1 is hydrogen, C_1 - C_4 alkyl, 1-(C_1 - C_4 alkoxy carbonyl)ethen-2-yl, phenyl
 10 optionally substituted with one or two substituents individually selected from the group consisting of halo, nitro, C_1 - C_4 alkoxy, C_2 - C_4 alkoxy substituted with piperidin-1-yl, and $-NR^5R^6$, pyridinyl, thiazolyl, or piperidin-4-yl optionally substituted at the 1-position with C_1 - C_4 alkoxy carbonyl or (C_1 - C_4 alkylene)- R^7 ;
- R^2 is phenyl optionally substituted with halo or trifluoromethyl;
- 15 R^3 is hydrogen or (C_1 - C_4 alkyl)sulfonyl;
- R^4 is halo or $-NR^8R^9$
- R^5 and R^6 are individually at each occurrence selected from hydrogen or C_1 - C_4 alkyl;
- R^7 is hydrogen, hydroxy, trifluoromethyl, or phenyl;
- 20 R^8 is hydrogen or C_1 - C_4 alkyl;
- R^9 is hydrogen, C_1 - C_4 alkyl, or benzyl;
- X-G-Y is $-N=C-N(R^{10})-$, $-N(R^{11})-C=N-$, or $-S-C=N-$;
- R^{10} is hydrogen or C_1 - C_4 alkyl;
- R^{11} is hydrogen, cyclohex-1-yl optionally substituted in the 4-position with
 25 hydroxy, amino, N-[C_1 - C_4 alkoxy carbonyl]amino, oxo, or ethylene glycol ketal, (C_1 - C_4 alkylene)- R^{12} , piperidin-4-yl optionally substituted at the 1-position with C_1 - C_4 alkyl or C_1 - C_4 alkoxy carbonyl, or 2,2,6,6-tetramethylpiperidin-4-yl;
- R^{12} is hydrogen, hydroxy, C_1 - C_4 alkoxy, C_1 - C_4 alkoxy carbonyl, N-[C_1 - C_4 alkoxy carbonyl]amino, C_3 - C_6 cycloalkyl, tetrahydropyran-4-yl, morpholin-4-yl, or phenyl
 30 optionally substituted with one or two substituents individually selected from halo;
 provided that when X-G-Y is $-N(R^{11})-C=N-$, then at least one of R^1 and R^{11} is hydrogen or

C₁-C₄ alkyl; or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable carrier, diluent or excipient.

6. A method of inhibiting p-38 kinase in a mammal comprising administering
5 to a mammal in need of such treatment an effective amount of a compound of Formula I:

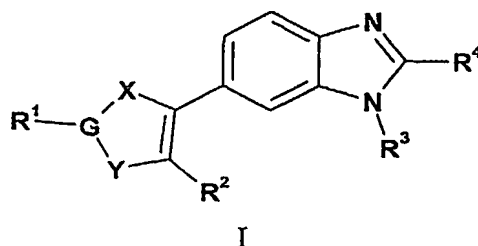


where:

- 10 R¹ is hydrogen, C₁-C₄ alkyl, 1-(C₁-C₄ alkoxy carbonyl)ethen-2-yl, phenyl optionally substituted with one or two substituents individually selected from the group consisting of halo, nitro, C₁-C₄ alkoxy, C₂-C₄ alkoxy substituted with piperidin-1-yl, and -NR⁵R⁶, pyridinyl, thiazolyl, or piperidin-4-yl optionally substituted at the 1-position with C₁-C₄ alkoxy carbonyl or (C₁-C₄ alkylene)-R⁷;
- 15 R² is phenyl optionally substituted with halo or trifluoromethyl;
R³ is hydrogen or (C₁-C₄ alkyl)sulfonyl;
R⁴ is halo or -NR⁸R⁹
R⁵ and R⁶ are individually at each occurrence selected from hydrogen or C₁-C₄ alkyl;
- 20 R⁷ is hydrogen, hydroxy, trifluoromethyl, or phenyl;
R⁸ is hydrogen or C₁-C₄ alkyl;
R⁹ is hydrogen, C₁-C₄ alkyl, or benzyl;
X-G-Y is -N=C-N(R¹⁰)-, -N(R¹¹)-C=N-, or -S-C=N-;
R¹⁰ is hydrogen or C₁-C₄ alkyl;
- 25 R¹¹ is hydrogen, cyclohex-1-yl optionally substituted in the 4-position with hydroxy, amino, N-[C₁-C₄ alkoxy carbonyl]amino, oxo, or ethylene glycol ketal, (C₁-C₄ alkylene)-R¹², piperidin-4-yl optionally substituted at the 1-position with C₁-C₄ alkyl or C₁-C₄ alkoxy carbonyl, or 2,2,6,6-tetramethylpiperidin-4-yl;
- 30 R¹² is hydrogen, hydroxy, C₁-C₄ alkoxy, C₁-C₄ alkoxy carbonyl, N-[C₁-C₄ alkoxy carbonyl]amino, C₃-C₆ cycloalkyl, tetrahydropyran-4-yl, morpholin-4-yl, or phenyl optionally substituted with one or two substituents individually selected from halo;

provided that when X-G-Y is -N(R¹¹)-C=N-, then at least one of R¹ and R¹¹ is hydrogen or C₁-C₄ alkyl; or a pharmaceutically acceptable salt thereof.

7. A method of treating conditions resulting from excessive cytokine
 5 production in a mammal comprising administering to a mammal in need of such treatment a cytokine-suppressing amount of a compound of Formula I



where:

- 10 R¹ is hydrogen, C₁-C₄ alkyl, 1-(C₁-C₄ alkoxy carbonyl)ethen-2-yl, phenyl optionally substituted with one or two substituents individually selected from the group consisting of halo, nitro, C₁-C₄ alkoxy, C₂-C₄ alkoxy substituted with piperidin-1-yl, and -NR⁵R⁶, pyridinyl, thiazolyl, or piperidin-4-yl optionally substituted at the 1-position with C₁-C₄ alkoxy carbonyl or (C₁-C₄ alkylene)-R⁷;
- 15 R² is phenyl optionally substituted with halo or trifluoromethyl;
 R³ is hydrogen or (C₁-C₄ alkyl)sulfonyl;
 R⁴ is halo or -NR⁸R⁹
 R⁵ and R⁶ are individually at each occurrence selected from hydrogen or C₁-C₄ alkyl;
- 20 R⁷ is hydrogen, hydroxy, trifluoromethyl, or phenyl;
 R⁸ is hydrogen or C₁-C₄ alkyl;
 R⁹ is hydrogen, C₁-C₄ alkyl, or benzyl;
 X-G-Y is -N=C-N(R¹⁰)-, -N(R¹¹)-C=N-, or -S-C=N-;
 R¹⁰ is hydrogen or C₁-C₄ alkyl;
- 25 R¹¹ is hydrogen, cyclohex-1-yl optionally substituted in the 4-position with hydroxy, amino, N-[C₁-C₄ alkoxy carbonyl]amino, oxo, or ethylene glycol ketal, (C₁-C₄ alkylene)-R¹², piperidin-4-yl optionally substituted at the 1-position with C₁-C₄ alkyl or C₁-C₄ alkoxy carbonyl, or 2,2,6,6-tetramethylpiperidin-4-yl;
 R¹² is hydrogen, hydroxy, C₁-C₄ alkoxy, C₁-C₄ alkoxy carbonyl, N-[C₁-C₄ alkoxy carbonyl]amino, C₃-C₆ cycloalkyl, tetrahydropyran-4-yl, morpholin-4-yl, or phenyl
 30 optionally substituted with one or two substituents individually selected from halo;

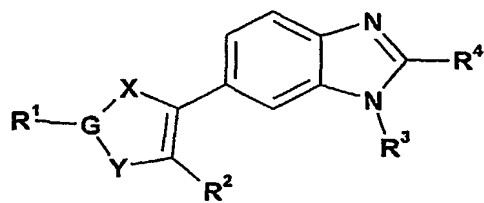
provided that when X-G-Y is $-N(R^I)-C=N-$, then at least one of R^I and R^{II} is hydrogen or C_1-C_4 alkyl; or a pharmaceutically acceptable salt thereof.

8. A method of Claim 7, where the cytokine is tumor necrosis factor α .



ABSTRACT

The present invention provides kinase inhibitors of Formula I:



I

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ **BLACK BORDERS**
- ☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- ☐ **FADED TEXT OR DRAWING**
- ☐ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- ☐ **SKEWED/SLANTED IMAGES**
- ☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- ☐ **GRAY SCALE DOCUMENTS**
- ☒ **LINES OR MARKS ON ORIGINAL DOCUMENT**
- ☐ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- ☐ **OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.